Attending: dr. Julia warren, medical oncology **Consultants:** dr. Benjamin torres (cardiology), dr. Amelia chen (pulmonology), dr. David patel (infectious disease

Discharge summary

Patient information

- **Name/id:** *Shruthi Howard (ID SYN*210*)*
- **Dob:** 1968-11-14
- **Age/sex:** 56f
- **Admission date:** 2025-04-02
- **Discharge date:** 2025-04-14
- **Length of stay:** 12 days

Principal diagnosis

Dabrafenib/trametinib-induced pyrexia syndrome with ards and transient cardiomyopathy in a patient with braf v600e-positive metastatic nsclc

Secondary diagnoses

1. Transient acute kidney injury (resolved)
2. Non-st elevation myocardial infarction (type 2)
3. Distributive shock (resolved)
4. Healthcare-associated pneumonia (resolved)
5. Hypokalemia (resolved)
6. Transaminitis (improving)

Comprehensive oncologic history

Patient is a 56-year-old female with braf v600e-positive metastatic non-small cell lung cancer diagnosed in april 2022. She initially presented with three months of progressive dyspnea and pleuritic chest pain. Imaging revealed a 3.7 cm left lower lobe mass with associated left pleural effusion and pleural nodularity.

Initial staging workup (april-may 2022):

- Pleural fluid cytology: positive for adenocarcinoma cells
- Thoracentesis with pleural biopsy: moderately differentiated adenocarcinoma
- Immunohistochemistry: ttf-1+, napsin a+, ck7+, ck20-, p40-
- Molecular testing:

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    - Braf v600e mutation positive
    - No other actionable mutations (egfr, alk, ros1, ret, met, ntrk all negative)
    - Pd-l1 expression: 70% tps, cps 80, ic 25%
- Pet/ct: fdg-avid left lower lobe mass (suv 14.2), pleural thickening, no distant metastases
- Mri brain: negative for metastases
- Stage: t2bn0m1a (stage iva) - malignant pleural effusion

Treatment course:

1. **First-line therapy (may 2022 - present):**
    - Combination therapy with dabrafenib 150 mg bid and trametinib 2 mg daily
    - Initiated 05/21/2022
    - Initial excellent response with near-complete resolution of pleural effusion by month 3
    - Primary tumor decreased by 70% at first restaging
    - Continued sustained response on subsequent scans
2. **Treatment complications and management:**
    - Grade 1 pyrexia syndrome (july 2022): managed with brief treatment interruption and acetaminophen
    - Grade 2 rash (september 2022): managed with topical steroids
    - Grade 2 pyrexia syndrome (november 2022): required 7-day treatment interruption and low-dose prednisone
    - Grade 2 transaminitis (february 2023): required 10-day treatment interruption
    - Grade 2 pyrexia syndrome (may 2023): required 14-day treatment interruption and prophylactic prednisone
    - Grade 3 pyrexia syndrome (august 2023): required hospitalization for 5 days
    - Dose reduction of dabrafenib to 100 mg bid (august 2023)
    - Grade 2 pyrexia syndrome (january 2024): managed with treatment interruption, resumed at reduced dose
    - Further dose reduction of dabrafenib to 75 mg bid (january 2024)
3. **Disease status prior to current admission:**
    - Most recent ct scan (march 2025): primary tumor stable at 1.1 cm (70% reduction from baseline)
    - No pleural effusion
    - No evidence of distant metastases
    - Ecog performance status 1 (baseline 0)

History of present illness

Patient presented to the emergency department on 04/02/2025 with three days of fever (maximum 40.2°c), rigors, progressive dyspnea, and generalized weakness. She reported adherence to dabrafenib 75 mg bid and trametinib 2 mg daily with no recent dose adjustments. She had been experiencing intermittent low-grade fevers (38-38.5°c) for approximately one week prior to presentation, managed with acetaminophen at home.

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However, symptoms acutely worsened with development of respiratory distress, prompting emergency evaluation.

On presentation, she was hypotensive (bp 82/45 mmhg), tachycardic (hr 128), febrile (t 39.8°c), and hypoxemic (spo_2 88% on room air). Initial laboratory studies showed elevated inflammatory markers, mild transaminitis, elevated troponin, and acute kidney injury. Chest imaging revealed bilateral patchy infiltrates consistent with ards. Braf-targeted therapy was immediately discontinued, and patient was admitted to the intensive care unit.

Hospital course

Critical care management (icu days 1-6):

- Initial management for presumed septic shock with fluid resuscitation and empiric broad-spectrum antibiotics (piperacillin-tazobactam and vancomycin)
- Required vasopressor support with norepinephrine for 48 hours
- Progressive hypoxemic respiratory failure requiring high-flow nasal cannula (up to 60l/min, fio_2 80%)
- Avoided mechanical ventilation with aggressive pulmonary toilet, proning, and diuresis
- Comprehensive infectious workup negative for bacterial, viral, or fungal pathogens
- Echocardiogram revealed newly reduced ejection fraction (35%, baseline 65%) with global hypokinesis
- Diagnosis of type 2 nstemi based on troponin elevation in setting of supply-demand mismatch
- Multidisciplinary discussion with cardiology, pulmonology, and infectious disease led to diagnosis of severe braf inhibitor-induced pyrexia syndrome with associated end-organ effects

Treatment approach:

- High-dose methylprednisolone (125 mg iv q6h × 48 hours, followed by taper)
- Aggressive temperature management with cooling measures and scheduled acetaminophen
- Conservative fluid management following initial resuscitation
- Continuation of empiric antibiotics until cultures negative at 72 hours
- Temporary withholding of all oncologic therapy

Icu to floor transition (day 7):

- Hemodynamic stability achieved with discontinuation of vasopressors
- Improved oxygenation with weaning to nasal cannula 4l
- Transition from iv to oral steroid taper
- Resumed oral intake with good tolerance

Floor management (days 8-12):

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- Gradual improvement in respiratory status with eventual discontinuation of supplemental oxygen
- Progressive improvement in renal function with medical management
- Repeated echocardiogram showed recovery of ejection fraction to 50%
- Continued steroid taper with clinical stability
- Developed healthcare-associated pneumonia on day 9, treated with ceftriaxone
- Multidisciplinary discussion regarding resumption of targeted therapy

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Diagnostic studies

Laboratory data:

Admission (04/02/2025):

- Wbc: 16.8 × 10^9/l (elevated)
- Hemoglobin: 12.8 g/dl
- Platelets: 265 × 10^9/l
- Sodium: 132 mmol/l (low)
- Potassium: 3.2 mmol/l (low)
- Chloride: 96 mmol/l
- Bicarbonate: 24 mmol/L

- BUN: 16 mg/dl
- Creatinine: 0.9 mg/dl
- Glucose: 124 mg/dl
- AST: 45 U/L
- ALT: 52 U/L
- Alkaline phosphatase: 98 U/L
- Total bilirubin: 0.8 mg/dl
- Albumin: 3.5 g/dl
- Troponin I: <0.04 ng/ml
- BNP: 245 pg/ml
- CRP: 18 mg/L

Microbiology:

- Blood cultures (×3): No growth
- Sputum culture (04/02/2025): Normal respiratory flora
- Sputum culture (04/11/2025): Light growth of Klebsiella pneumoniae, sensitive to ceftriaxone
- Urine culture: No growth
- Respiratory viral panel: Negative
- COVID-19 PCR: Negative
- Fungal studies: Negative

Imaging:

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Chest X-ray (04/02/2025): Bilateral diffuse interstitial and alveolar infiltrates, most prominent in the bases. No pleural effusion.

CT Chest without contrast (04/03/2025): Bilateral ground-glass opacities with dependent consolidations consistent with ARDS. Stable left lower lobe mass (1.1 cm) compared to prior imaging. No evidence of pulmonary embolism.

Chest X-ray (04/14/2025): Significant improvement in bilateral airspace opacities. Residual bibasilar atelectasis.

CT Chest/Abdomen/Pelvis with contrast (04/12/2025):

- Resolution of ground-glass opacities
- Stable left lower lobe nodule (1.1 cm)
- No pleural or pericardial effusion
- No evidence of new metastatic disease
- No lymphadenopathy

Cardiac Studies:

Electrocardiogram (04/02/2025): Sinus tachycardia, rate 124. Nonspecific T-wave inversions in lateral leads. No acute ST changes.

Transthoracic Echocardiogram (04/03/2025):

- LVEF 35% (reduced from 65% on study from 01/2024)
- Global hypokinesis
- No significant valvular disease
- No pericardial effusion
- No evidence of wall motion abnormalities suggestive of coronary artery disease

Repeat Echocardiogram (04/11/2025):

- LVEF recovered to 50%
- Mild global hypokinesis
- Otherwise unchanged

MULTIDISCIPLINARY DISCUSSION AND RECOMMENDATION

A multidisciplinary tumor board discussion on 04/12/2025 included medical oncology, cardiology, pulmonology, clinical pharmacy, and infectious disease. The consensus opinion was that the patient experienced severe dabrafenib/trametinib-induced pyrexia syndrome with multi-organ involvement, including ARDS and cardiomyopathy.

Given the following factors:

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1. Excellent ongoing disease control with BRAF-targeted therapy
2. Progressive pattern of pyrexia syndrome with increasing severity despite dose reductions
3. Life-threatening nature of current episode
4. Recovery of organ function
5. Limited alternative therapeutic options

The recommendation was to:

1. Permanently discontinue dabrafenib/trametinib combination
2. Consider transition to alternative BRAF-directed therapy after full recovery
3. Options include: a. BRAF inhibitor monotherapy (vemurafenib or encorafenib) at reduced dose b. Immune checkpoint inhibitor (high PD-L1 expression may predict response) c. Clinical trial of novel BRAF inhibitor with different toxicity profile
4. Complete steroid taper before initiating new therapy
5. Baseline cardiac and pulmonary function testing before next therapy

Patient was counseled on these recommendations and elected to try BRAF inhibitor monotherapy with close monitoring after a 3-week treatment holiday.

DISCHARGE PLAN

Medications:

1. Prednisone 20 mg PO daily × 3 days, then 10 mg daily × 3 days, then 5 mg daily × 3 days, then discontinue
2. Ceftriaxone 1 g IV daily × 3 more days (complete 7-day course)
3. Pantoprazole 40 mg PO daily
4. Acetaminophen 650 mg PO q6h PRN temperature >38.0°C
5. Metoprolol succinate 25 mg PO daily
6. Resume home medications except dabrafenib and trametinib (HOLD)

Follow-up Appointments:

1. Medical Oncology: Dr. Warren in 1 week (04/21/2025)
2. Cardiology: Dr. Torres in 2 weeks (04/28/2025)
3. Pulmonology: Dr. Chen in 2 weeks (04/28/2025)

Testing:

1. Comprehensive metabolic panel and CBC in 1 week
2. Repeat echocardiogram in 4 weeks
3. Pulmonary function tests in 4 weeks
4. Restaging CT chest/abdomen/pelvis in 6 weeks

Return Precautions:

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1. Fever >38.0℃
2. Shortness of breath, chest pain
3. Palpitations or lightheadedness
4. Rash or other new symptoms

Next Treatment Plan:

1. 3-week treatment holiday from all anticancer therapy
2. Consider encorafenib monotherapy at reduced dose (planned start 05/05/2025)
3. Premedication with antihistamines and antipyretics for first month
4. Low threshold for treatment interruption with any fever

CONDITION AT DISCHARGE

Patient is afebrile, hemodynamically stable, and in no respiratory distress. Ambulating independently. ECOG performance status 2 (from baseline 1). Complete resolution of organ dysfunction with laboratory values normalizing or improving. Continued mild fatigue expected to improve with full recovery.

Electronically signed by:

Julia Warren, MD
Medical Oncology
04/14/2025 17:30

Benjamin Torres, MD
Cardiology
04/14/2025 16:45

Amelia Chen, MD
Pulmonology
04/14/2025 15:20