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Utility of a Diagnostic Time-Out to Evaluate an Atypical Pneumonia

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PRESENTATION

A 48-year-old woman with no significant medical history presented to the emergency department with fever, non-productive cough, and shortness of breath for 4 days. She reported ongoing dyspnea on exertion over 1 month, which rapidly progressed in the days leading up to her presentation. She also reported experiencing watery, non-bloody diarrhea, night sweats, and ageusia in the past month. A review of systems was negative for weight loss, headache and neck pain, chest pain, rash, lymphadenopathy, arthralgia, dysuria, and change in urinary frequency. The patient worked as a meat cutter at a local grocery store in Maryland and did not report any sick contacts, recent travel, or illicit substance use. Her vaccinations were up to date, including the coronavirus disease (COVID-19) vaccine, which she received 2 months prior to presentation.

ASSESSMENT

She was febrile (temperature 38.1 C), tachypneic with oxygen saturation of 88% and tachycardic (heart rate 117 beats/min, blood pressure 106/71 mm Hg). A pulmonary exam was notable for diffuse, coarse crackles bilaterally, and she was in respiratory distress (respiratory rate 20 breaths/min), requiring 2 liters of supplemental oxygen. Wheezing, intercostal retractions, and fingernail clubbing were absent. Her complete blood count showed hemoglobin of 9.9 g/dL (reference 12-16 g/dL) and normal white blood cell count with neutrophilia (83.6%, reference 40%-60%) and lymphopenia (5.5%, reference 20%-40%) (Table). Serum electrolytes, liver enzymes, blood urea nitrogen, and creatinine were within normal limits. Inflammatory markers, such as

C-reactive protein (14.6 mg/dL, reference < 10 mg/dL) and erythrocyte sedimentation rate (114 mm/h, reference < 29 mm/h), were elevated, and a COVID-19 nasal swab was negative. A chest x-ray demonstrated prominent central bronchovascular markings (Figure 1A). A computed tomography scan without contrast of the thorax revealed diffuse, symmetric bilateral ground-glass opacities most prominent at the lung bases (Figure 1B). Given that the presentation was most consistent with community-acquired viral or atypical pneumonia, she was admitted to the hospital and was initiated on intravenous antibiotics for pneumonia. The diagnostic workup included 2 sets of peripheral blood cultures, sputum culture, *Streptococcus pneumoniae* and *Legionella* urine antigen and a comprehensive respiratory virus panel test (including a repeat SARS-CoV-2), all of which were negative.

After 2 days, her fever persisted with a maximum temperature of 39.4 C, and her clinical status deteriorated with progressive fatigue, intermittent episodes of confusion, and increasing oxygen requirement up to 6 liters. A repeat computed tomography scan of her lungs to evaluate for pulmonary embolism and progression of pneumonia revealed worsening lung opacities but no evidence of pulmonary embolism (Figure 1B).

DIAGNOSIS

The initial diagnosis of pneumonia seemed an adequate fit given the opacities on chest imaging and the clinical syndrome that included fever, dyspnea, and cough.¹ Her history of extrapulmonary symptoms (diarrhea, night sweats, ageusia) suggested an atypical pneumonia. Because of the current pandemic, we were most suspicious of COVID-19 pneumonia; however, this was ruled out by 2 polymerase chain reaction tests performed a day apart. The patient's worsening status then prompted a diagnostic time-out, and reevaluation of her history, which revealed that her husband was human immunodeficiency virus (HIV) positive and non-adherent to antiretroviral therapy. Subsequently, a hypothesis driven

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Table Pertinent Laboratory Values Including the Complete Blood Count, Complete Metabolic Profile, and Inflammatory Markers, Measured at Presentation and Date of Discharge

Lab Value	Reference	Presentation	Discharge
Complete Blood Count			
Red Blood Cell Count	4.00 - 5.20 (K/mm ³)	3.6	3.56
Hemoglobin	12 - 16 (g/dL)	9.9	10.6
White Blood Cell Count	4.50 - 11.00 (K/mm ³)	7.07	4.8
Neutrophil	40 - 60 (%)	83.6	77.6
Lymphocyte	20 - 40 (%)	5.5	7.3
Absolute Neutrophil Count	1.50 - 7.80 (K/mm ³)	5.89	3.73
Absolute Lymphocyte Count	1.10 - 4.80 (K/mm ³)	0.39	0.35
Complete Metabolic Panel			
Serum Electrolytes			
Sodium	136 - 145 (mmol/L)	139	138
Potassium	3.5 - 5.1 (mmol/L)	4	3.8
Chloride	98 - 107 (mmol/L)	107	106
Carbon Dioxide	21 - 32 (mmol/L)	26	23
Urea Nitrogen	7 - 18 (mg/dL)	7	19
Creatinine	0.60 - 1.30 (mg/dL)	1	0.92
Glucose	71 - 99 (mg/dL)	94	78
Calcium	8.5 - 10.1 (mg/dL)	8.5	8.5
Liver Enzymes			
Alkaline Phosphatase	45 - 117 (U/L)	116	75
Aspartate Amino Transferase	3 - 37 (U/L)	69	28
Alanine Amino Transferase	6 - 65 (U/L)	32	19
Inflammatory Markers			
Erythrocyte Sedimentation Rate	4 - 25 (mm/h)	114	-
C-Reactive Protein	<0.29 (mg/dL)	14.6	-
Other			
HIV-1/2 Antibodies	Nonreactive	HIV-1 Reactive	
CD3+ lymphocytes	51 - 91 (%)	58.2	
CD4+ lymphocytes	32 - 68 (%)	2	
Absolute CD4+ lymphocytes	458 - 1344/mm ³	7	
Lactate Dehydrogenase	100 - 190 U/L	471	

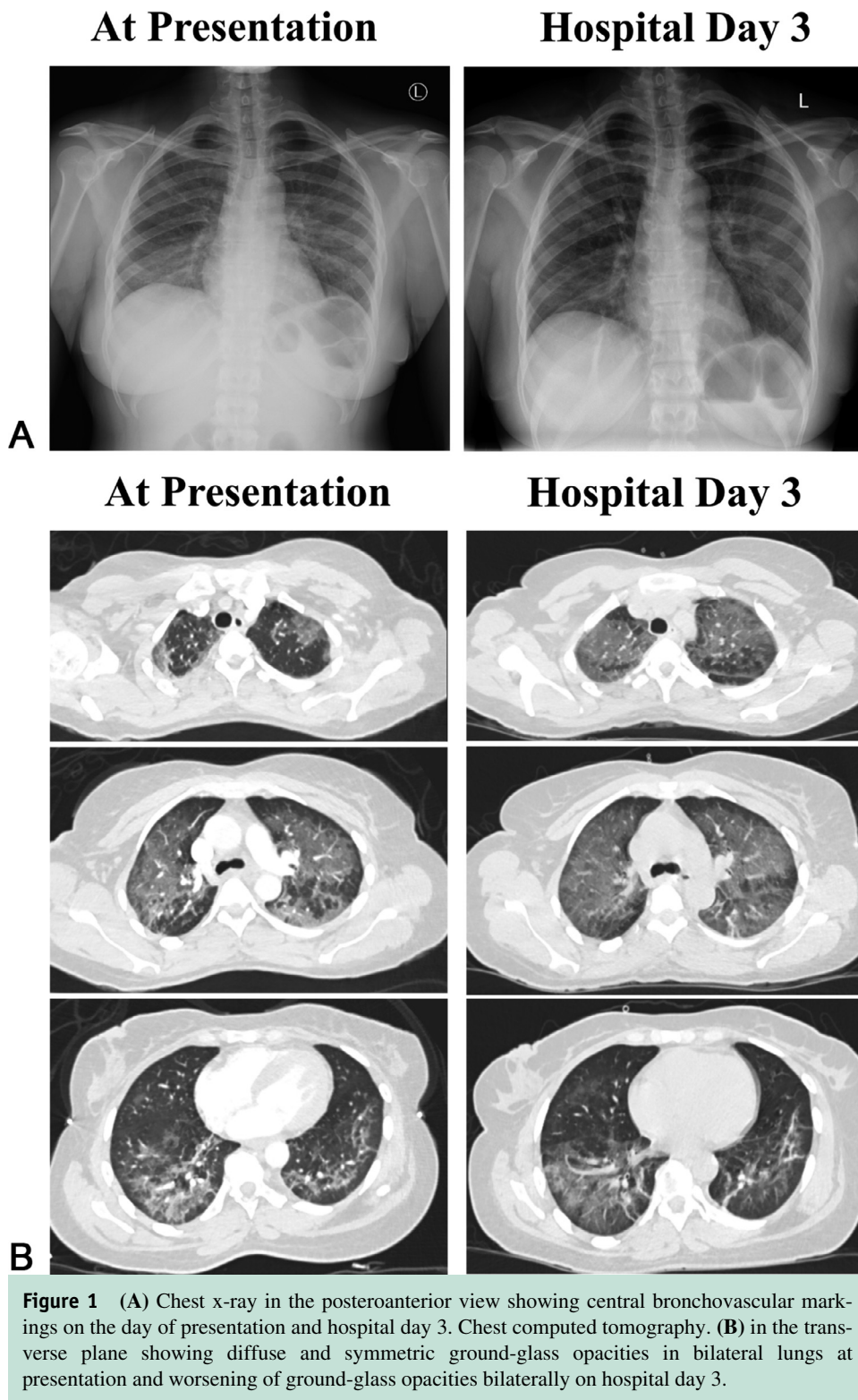
physical exam revealed pseudomembranous, white patches on the tongue most consistent with oral candidiasis (Figure 2), driving us to consider immunocompromised states in our differential diagnosis. The HIV polymerase chain reaction test returned positive with a CD4 count of 7 (normal 500-1200 cells per cubic millimeter, cells/mm³) and a lactate dehydrogenase level that was elevated (Table).

A diagnosis of *Pneumocystis jirovecii* pneumonia was confirmed by bronchoscopy with bronchoalveolar lavage, which is the gold-standard diagnostic test (sensitivity of 90%-98% and specificity of 83%-96%).² Given an acute change in the patient's mental status, lumbar puncture and head imaging were also performed to rule out meningoencephalitis. Brain magnetic resonance imaging revealed non-specific, diffuse ischemic changes, and a lumbar puncture was negative for infection in the cerebrospinal fluid.

Pneumocystis jirovecii pneumonia is a life-threatening fungal pneumonia caused by *P jirovecii*, which typically occurs in immunocompromised individuals and remains a prevalent opportunistic infection in HIV-infected individuals, comprising 20% of pulmonary infiltrates of infectious

etiology.² Other risk factors for this opportunistic infection include malignancy, hematopoietic stem cell or solid organ transplantation, and medications such as glucocorticoids or immunosuppressive therapies (eg, cyclosporine).³ *Pneumocystis* is thought to be transmitted through airborne droplets. Immunocompetent individuals, although typically not affected, may serve as reservoirs for spread to immunocompromised hosts.⁴

Pneumocystis jirovecii pneumonia in an HIV-infected individual commonly presents with progressive dyspnea in the setting of fever and non-productive cough. It typically appears on chest radiograph as bilateral perihilar interstitial infiltrates (referred to as "ground-glass opacities"). Detection of *Pneumocystis jirovecii* on bronchoalveolar lavage is the gold-standard for diagnosis and provides the highest diagnostic yield in infected individuals.⁵ Trimethoprim-sulfamethoxazole is the most effective treatment for *P jirovecii* pneumonia⁴; the adjunctive use of corticosteroids reduces mortality and the need for mechanical ventilation in patients with hypoxemia (partial pressure of arterial oxygen less than 70 mm Hg or alveolar-arterial gradient above 35).⁶



Utility of Diagnostic Time-Out

According to the dual process theory of decision-making, physicians rely on 2 types of reasoning models in the diagnosis and management of patients: analytic and intuitive.⁷ In the analytic model, physicians employ a time-consuming

process in generating a broad differential diagnosis and a deliberate evaluation of hypotheses. In contrast, the intuitive model relies on pattern-recognition refined by knowledge of typical and atypical presentations and clinical experience. Through this case report, we offer an approach



Figure 2 Pseudomembranous, white patches on the patient's tongue most consistent with oral candidiasis.

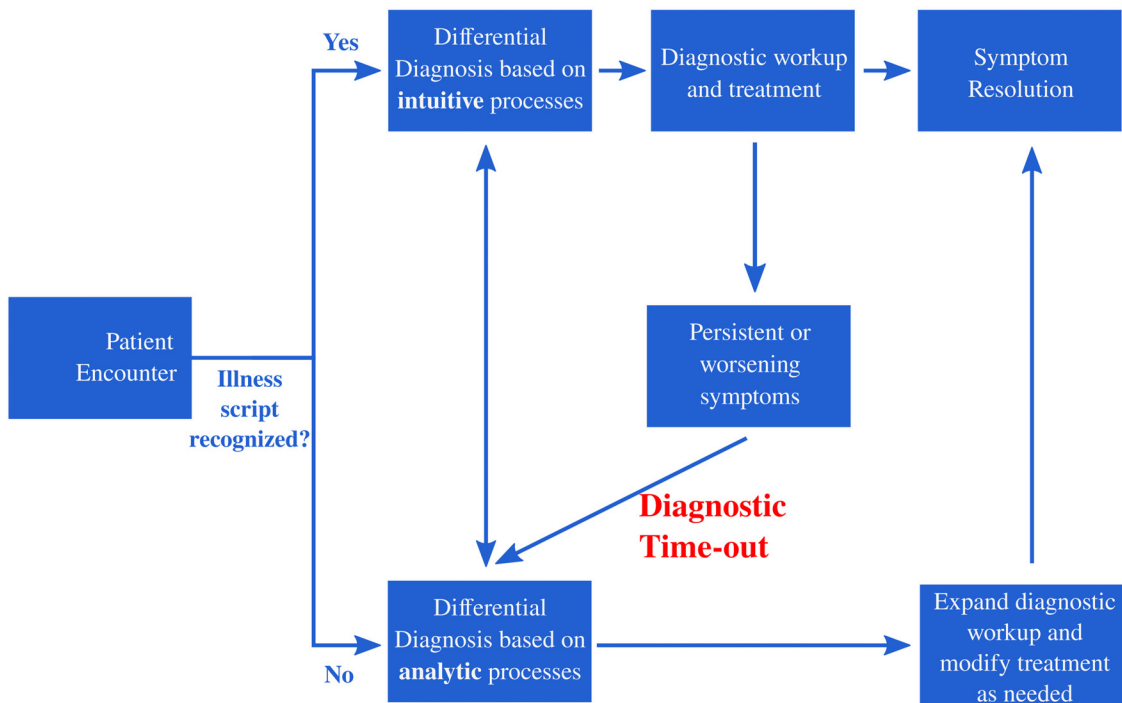


Figure 3 Schema for developing and reflecting on the working diagnosis.

to improve the diagnostic process by utilizing a diagnostic time-out (Figure 3). This approach enables the clinician to reflect on potential gaps in data gathering, the impact of cognitive biases, and embarking on plans with structured follow-ups.⁸ Returning to the bedside to gather a hypothesis-driven history and to perform a comprehensive exam may prompt the discovery of key findings, as illustrated by the patient's oropharyngeal candidiasis and a history of HIV infection in her spouse.

MANAGEMENT

The patient was initiated on a 21-day course of oral trimethoprim-sulfamethoxazole (800 mg trimethoprim, 160 mg sulfamethoxazole) twice a day and a prednisone taper, in addition to anti-retroviral therapy, in accordance with current Centers for Disease Control and Prevention guidelines for patients with a CD4 count less than 200 cells/mm³.⁹ Two weeks after discharge at a follow-up appointment with her primary care provider, she reported resolution of symptoms and adherence to anti-retroviral therapy.

In conclusion, this case demonstrates that a diagnostic time-out can help avoid delay in appropriate care and consequently improve the patient's clinical trajectory.

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