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Adenosine Deaminase Diagnostic Testing in Pericardial Fluid

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Abstract

A 65-year-old Vietnamese man with hypertension, type 2 diabetes mellitus, and chronic hepatitis B with cirrhosis presented with a 2-week history of shortness of breath at rest, orthopnea, and lower extremity edema. He reported a 4-month history of nonproductive cough, 5-kg weight loss, and fatigue. He immigrated to the United States as an adult more than 20 years before presentation. His temperature was 37°C, heart rate was 78/min, respiratory rate was 17/min, and blood pressure was 158/95 mm Hg. A chest radiographic image suggested cardiomegaly and a computed tomographic scan demonstrated a moderate to large pericardial effusion. A pericardial drain was placed and pericardial fluid was sent to the laboratory for evaluation. Initial pericardial fluid study results are presented in the Table. Empirical treatment for tuberculosis was initiated. Three days later, an adenosine deaminase (ADA) level of 118.1 U/L (normal range, 0.0–11.3 U/L) from pericardial fluid was reported from the laboratory.

Answer

B. Stop further nontubercular diagnostic testing and continue antitubercular therapy

Test Characteristics

ADA is an enzyme in lymphocytes and myeloid cells that recycles toxic purine pathway metabolites, which are essential for DNA metabolism and cell viability.^{1,2} ADA levels are elevated in inflammatory effusions, including pleural, pericardial, and joint effusion, caused by bacterial infections, granulomatous inflammation (eg, tuberculosis, sarcoidosis), malignancy, and autoimmune diseases (eg, lupus, vasculitis).^{1,2} ADA is normally elevated in neutrophil-predominant effusions and is not a useful diagnostic test in the setting of neutrophil-predominant effusions.³ However, among lymphocyte-predominant effusions, levels of ADA are typically higher in those caused by tuberculosis (TB) than those caused by other conditions.^{1,2}

In lymphocyte-predominant effusions, the most common threshold for an ADA test result indicating TB is an ADA level greater than 40 U/L. An ADA level greater than 40 U/L has a

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sensitivity of 87% to 93% and specificity of 89% to 97% for TB.^{2,4} At a threshold of greater than 35 U/L, sensitivity is higher (93%-95%) but specificity is lower (74%-90%).^{3,5,6} Given a pretest probability of 70% for TB in a lymphocyte-predominant pericardial effusion in a patient from an endemic country,⁷ an ADA level greater than 40 U/L results in a posttest probability of 96%, while a level less than or equal to 40 U/L results in a posttest probability of 19%. The Centers for Medicare & Medicaid Services reimbursement rate for ADA testing is \$8.10 (Current Procedural Terminology code 84311).

Application to This Patient

In the current patient, the ADA test was ordered from pericardial fluid to confirm the presumptive diagnosis of pericardial TB, for which antitubercular therapy was initiated. RIPE (rifampin, isoniazid, pyrazinamide, ethambutol) therapy was started because of the high pretest probability of TB in a patient from a country with endemic TB with chronic cough, weight loss, and lymphocyte-predominant pericardial effusion. The patient's ADA level of 118.1 U/L confirmed the diagnosis, enabling cessation of further evaluation and supporting continuation of antitubercular therapy.

An alternative approach is to await a culture positive for TB before starting therapy. However, cultures positive for TB can take weeks to grow, which can allow infection to progress while awaiting confirmation. An ADA level greater than 40 U/L in a patient with a high pretest probability of disease results in a sufficiently high posttest probability to justify a full course of TB therapy. Furthermore, even with an ADA level less than or equal to 40 U/L in a patient with a high pretest probability, the posttest probability of approximately 20% is sufficiently high to warrant empirical therapy. However, the low ADA level would necessitate further diagnostic testing, including invasive pericardial biopsy and serologies, to rule out other causes (eg, sarcoid, malignancy, vasculitis) while treating the patient for TB. In that situation, empirical TB therapy could have been stopped if an alternative diagnosis was established.

What Are Alternative Diagnostic Testing Approaches?

Elevated interferon- γ concentrations in effusions have high sensitivity (95.7%) and specificity (96.3%) for active TB, but their use is limited by cost and availability.^{1,4} Interferon- γ can also be measured from whole blood via IGRAs. However, IGRAs and the similar purified protein derivative skin test are only useful to diagnose latent TB. Laboratory test results indicating ADA values greater than 40 U/L cannot distinguish between latent and active TB (nonspecific), and IGRAs/purified protein derivatives are associated with false-negative results in up to 30% of patients with pulmonary TB and 50% of patients with disseminated TB,^{8,9} because active TB causes antigen-specific anergy of T cells.

Patient Outcomes

The patient's sputum was negative for acid-fast bacilli smears and TB polymerase chain reaction. Pericardial fluid cytology demonstrated inflammatory cells, but was negative for malignant cells, acid-fast bacilli stain, and TB polymerase chain reaction. However, the

pericardial fluid cultures grew TB at 3 weeks and the sputa cultures grew TB at 5 weeks. Seven months after the start of treatment, the patient was hospitalized and died of complications of pneumonia and septic shock unrelated to TB.

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WHAT WOULD YOU DO NEXT?

- A.** Perform additional pericardial effusion cytology and culture testing
- B.** Stop further nontubercular diagnostic testing and continue antitubercular therapy
- C.** Initiate oral colchicine, nonsteroidal anti-inflammatory drugs, and steroids for systemic inflammation
- D.** Perform an interferon- γ release assay (IGRA)

Clinical Bottom Line

- ADA levels are typically elevated, and not diagnostically helpful, in neutrophil-predominant effusions.
- In lymphocyte-predominant effusions, ADA levels are elevated in effusions caused by tuberculosis, but typically not in effusions due to other diseases.
- In a patient with a low pretest probability of TB, an ADA level less than or equal to 40 U/L in a lymphocyte-predominant effusion essentially rules out TB.
- In a patient with a high pretest probability of pericardial TB, an ADA level greater than 40 U/L in a lymphocyte-predominant effusion is highly suggestive of TB, precluding the need for further diagnostic testing.

Pericardial Fluid Laboratory Results

Table.

Variable	Result	Normal Value or Reference Range
Color	Yellow	Clear to straw yellow
Clarity	Moderate cloudy	Clear
Glucose, mg/dL	49 (vs 117 in blood)	Parallel to serum values
Protein, g/dL	5.6	No reference range established
Nucleated cell count, / μ L	2035	<300
Segmented neutrophils	8%	0
Lymphocytes	58%	0
Monocytes/histiocytes	34%	0

SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; protein to g/L, multiply by 10.0.