

JAMA Diagnostic Test Interpretation

Evaluating the Erythrocyte Sedimentation Rate

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A healthy 65-year-old woman presented with 2 days of sustained throbbing, bilateral temporal headache and bilateral blurred vision. Laboratory results are shown in the Table. Given her erythrocyte sedimentation rate (ESR) of 110 mm/h and symptoms concerning for giant cell arteritis (GCA), a temporal artery biopsy was obtained. Results showed a normal caliber lumen without infiltrating inflammatory cells.

Table. Patient's Laboratory Values

| Laboratory Test | Patient's Values | Reference Value or Range |
|--|------------------|---|
| White blood cell count, $\times 10^3/\mu\text{L}$ | 4.1 | 3.5-10.5 |
| Hemoglobin, g/dL | 11.3 | 11.6-15.4 |
| Platelet count, $\times 10^3/\mu\text{L}$ | 171 | 140-390 |
| Serum | | |
| Sodium, mEq/L | 137 | 135-145 |
| Potassium, mEq/L | 4.1 | 3.5-4.5 |
| Chloride, mEq/L | 110 | 96-106 |
| Bicarbonate, mEq/L | 25 | 23-29 |
| Calcium, mg/dL | 9.2 | 8.5-10.2 |
| Albumin, g/dL | 3.8 | 3.5-5.5 |
| Total protein, g/dL | 10.4 | 6.0-8.3 |
| Erythrocyte sedimentation rate (Westergren method), mm/h | 110 | Men: $< \text{age} / 2$ Women: $< (\text{age} + 10) / 2$ |
| C-reactive protein, mg/L | 2.8 | < 3.0 |

SI conversion factors: To convert hemoglobin, albumin, and total protein to g/L, multiply by 10; sodium, potassium, chloride, and bicarbonate to mmol/L, multiply by 1.0; C-reactive protein to nmol/L, multiply by 9.424.

WHAT WOULD YOU DO NEXT?

- A. Brain magnetic resonance imaging
- B. Empirical methotrexate prescription
- C. Empirical sumatriptan prescription
- D. Serum protein electrophoresis (SPEP)

Answer

D. Serum protein electrophoresis (SPEP)

While the patient had a nearly 50% pretest probability of GCA,¹ the negative predictive value of temporal artery biopsy is approximately 83%.^{2,3} The negative biopsy results required consideration of an alternative diagnosis, such as brain abscess, cerebral venous sinus thrombosis, or hypergammaglobulinemia with hyperviscosity. The high ESR, low anion gap (2 mEq/mL), and elevated globulin gap (6.6 g/dL) support a diagnosis of hypergammaglobulinemia. Empirical steroids are recommended when GCA is strongly suspected, even before temporal artery biopsy, but were not prescribed because of high suspicion for the alternative diagnosis of hypergammaglobulinemia.

Test Characteristics

The ESR measures the rate at which red blood cells (RBCs) settle in the plasma of anticoagulated blood in a standardized Westergren tube (Figure). Although the ESR is considered a measure of inflammation from infection, malignancy, or rheumatologic disease, multiple non-inflammatory factors affect RBC sedimentation. These factors alter the ESR via distinct mechanisms: spatial interference, electrical charge, and viscosity (Supplement).⁴ Increased spatial interference, defined as physical factors interfering with the ability of RBCs to settle in

the Westergren tube, slows the packing of erythrocytes at the tube bottom, thereby decreasing the ESR. With extreme leukocytosis, RBC downward flow is impeded by leukocytes, which decreases the ESR.⁵ Conversely, decreased spatial interference, such as with cases of anemia and consequently fewer RBCs, causes an increase in the ESR because RBCs can sediment with less obstruction.⁴ Electrical charge refers to the slight negative surface charge that RBCs have, which causes them to repel each other, impeding erythrocyte packing and sedimentation.^{5,6} However, if plasma is enriched with positively charged proteins, such as immunoglobulins or fibrinogen, this electrical repulsion is blunted and RBC agglutination occurs, speeding sedimentation.⁴ Fibrinogen is a large, positively charged protein and the most abundant acute-phase reactant. Elevated fibrinogen is the predominant reason for high ESR in inflammatory states.^{4,5,7} Increased plasma viscosity, such as in cases of hypergammaglobulinemia, can slow erythrocyte sedimentation through the plasma and decrease the ESR.^{4,8}

Because noninflammatory factors influence the ESR, its specificity for establishing a diagnosis of inflammatory conditions is modest. In an analysis of 1106 patients who underwent 1174 temporal artery biopsies, an ESR value greater than 22 mm/h in men and 29 mm/h in women had sensitivity of 84.2%, specificity of 29.5%, positive predictive value of 26.4%, and negative predictive value of 86.1% for a diagnosis of GCA.⁹ In another study,¹⁰ using a higher ESR cutoff improved specificity, but sensitivity markedly decreased; an ESR cutoff of greater than

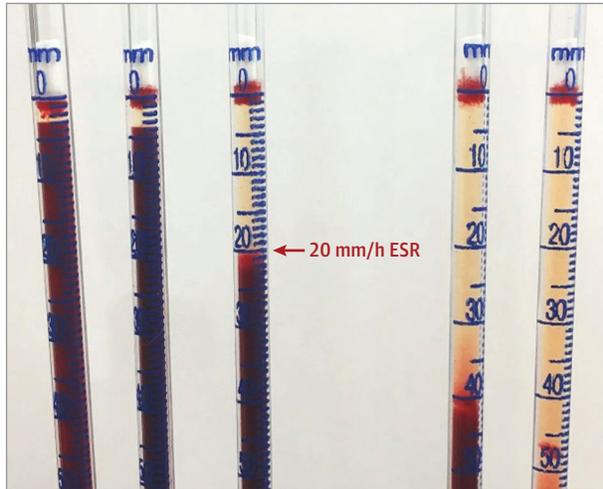


Figure. The erythrocyte sedimentation rate (ESR) is the distance (mm) that anticoagulated blood settles into the red blood cell and plasma components over 1 hour. The middle tube demonstrates an ESR of 20 mm/h.

107 mm/h had a sensitivity of 23%, specificity of 90.1%, positive predictive value of 30%, and negative predictive value of 86.5% for a diagnosis of GCA (positive and negative predictive values calculated by the authors from data provided by Walvick)¹⁰. In a study of 1006 patients, ESR greater than 100 mm/h had poor sensitivity for infection (36%), malignancy (25%), and inflammatory disorders (21%). However, it had high specificity (99%) for elevated sickness index, defined as the presence of a significant underlying disease.⁶ These results suggest an ESR greater than 100 mm/h deserves diagnostic attention but is non-specific and cannot by itself establish a diagnosis. Common causes of ESR greater than 100 mm/h include deep-seated infection, such as endocarditis or osteomyelitis; connective tissue disorders, such as GCA; and malignancies, such as multiple myeloma and Waldenström macroglobulinemia.⁴ The ESR cost to Medicare is \$3.33.

Application of Test Results to This Patient

The patient's high ESR was related to noninflammatory factors. The low anion gap and elevated globulin gap suggested elevated paraproteins. SPEP results showed a monoclonal IgM concentration of

1260 mg/dL (reference range, 48-271 mg/dL). Because γ -globulins are positively charged plasma proteins, the repelling force of the negative surface charge of RBCs is blunted in hypergammaglobulinemia, which facilitates agglutination of RBCs and rapid sedimentation. The patient's blood viscosity relative to water was 4.1 (reference range, 1.4-1.8). Although hyperviscosity decreases the ESR, the electrical charge effect of hypergammaglobulinemia is stronger, hence the patient's ESR of 110 mm/h.⁴ Bone marrow biopsy results showed 10% K-restricted lymphoplasmacytic cells, confirming Waldenström macroglobulinemia. The patient's presenting symptoms of headache and blurry vision are common presentations of this disease.

Alternative Diagnostic Testing Approaches

In scenarios with high suspicion for GCA but negative temporal artery biopsy results, a second, contralateral biopsy can be considered. Approximately 5% of these contralateral biopsies will be positive when the first was negative.^{2,3} C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver. CRP is elevated with most inflammatory conditions but is unaffected by noninflammatory factors.⁷ The patient had a normal CRP level, highlighting the noninflammatory cause of her elevated ESR. Obtaining concurrent ESR and CRP levels is less cost-effective than obtaining one before the other, but may provide benefit in select cases.

Patient Outcome

The patient was treated with rituximab and has been in remission for 3 years. Her IgM concentration decreased to 261 mg/dL and her ESR decreased to 32 mm/h.

Clinical Bottom Line

- Although commonly used to measure inflammation, the ESR is affected by noninflammatory factors, including anemia, polycythemia, hypofibrinogenemia or hyperfibrinogenemia, and hypergammaglobulinemia.
- Patients with ESR greater than 100 mm/h are likely to have a clinically relevant underlying condition, but the ESR test is nonspecific.
- Understanding the physiologic principles of erythrocyte sedimentation can facilitate the diagnosis of underlying etiologies.

ARTICLE INFORMATION

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