

Q: What evaluation should be done for an apparently healthy patient with an increased mean corpuscular volume (MCV)?

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A: INCREASED MEAN CORPUSCULAR volume (MCV) can be a sign of a wide variety of conditions (TABLE 1). Most are linked to defects in bone marrow DNA synthesis that prevent cell division and produce abnormally large erythrocytes. For a patient who is generally healthy, a careful history (TABLE 2) and physical examination may reveal apparently trivial symptoms that can lead to the correct diagnosis.

■ VITAMIN DEFICIENCIES

Elevated MCV may be caused by deficiencies of vitamin B₁₂ (cobalamin) or folate. The elevation may be the first abnormality in the hematological picture, but on careful examination, patients may show other clinical manifestations of vitamin deficiency,¹ such as decreased vibratory sense. Some patients may report subtle memory loss or peripheral sensory deficits.

■ MYELODYSPLASIA

When elevated MCV is accompanied by anemia, leukopenia, or thrombocytopenia, suspect myelodysplasia.^{2,3} Patients with early myelodysplasia may consider themselves asymptomatic but when questioned may report fatigue or easy bruising. Reviewing the peripheral blood smear and performing a bone marrow exam may be necessary for a diagnosis. The optimal timing of the bone marrow analysis is difficult to determine: performing it too early in the course of disease may yield equivocal findings, but waiting too long may delay needed therapy.

TABLE 1

Causes of increased MCV*

Nutritional deficiencies

- Folate deficiency
- Vitamin B₁₂ deficiency

Myelodysplasia

Alcohol consumption

Reticulocytosis

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Structural variants of alpha or beta globin chains
- Sickle cell disease (unusual cause of elevated MCV)
- Cytoskeletal defects
- Enzymopathies
- Chronic hemolytic anemias
- Runner's macrocytosis

Drugs

- Antimetabolites
- Alkylating agents
- Heavy metals
- Drugs that lead to hemolysis such as methyldopa
- Antiretroviral agents
- Herbal remedies

Laboratory artifacts

- Cold agglutinins
- Rouleaux

Malabsorption syndromes

- Celiac disease
- Lymphoma of the gut
- Amyloid infiltration of the gut
- Lymphangiectasia
- Whipple disease

Trauma to red blood cells

- Abnormally seated prosthetic heart valves
- Regurgitant jets

*Listed in approximate order of frequency

TABLE 2

Important points in the history from patients with elevated MCV

- Check previous complete blood count results and previous MCVs for trend over time
- Ask about symptoms suggesting anemia, such as tiredness, shortness of breath, feeling cold
- Determine alcohol intake
- Determine dietary history
- Evaluate for neurologic abnormalities
 - Memory loss
 - Gait disturbance
 - Neuropathic symptoms
- Ask about medication history

■ ALCOHOL CONSUMPTION

If the MCV is slightly elevated and nothing else is wrong with the complete blood count, alcohol consumption should be considered.^{4,5}

The amount of alcohol necessary to induce this elevation in MCV is difficult to quantify. Patients often underestimate their true consumption. “A few beers on the weekend” or “a glass of wine with dinner” may be enough to increase the MCV in a person with otherwise-normal nutrition.

■ CHRONIC MCV ELEVATION

It is very important to examine the patient’s records to identify chronic elevations or slowly rising MCV over time.

Gradual increases over time imply a slowly changing clinical situation, such as a progressive myelodysplasia or an increase in the patient’s alcohol consumption over time. Chronic MCV elevation (from birth through adulthood) is more likely to be observed in hereditary conditions such as cytoskeletal defects.

Hemolytic anemia

Chronic elevated MCV might indicate an underlying well-compensated hemolytic anemia that causes a chronic elevated reticulo-

cyte count; this would increase MCV because reticulocytes are larger than mature red blood cells.

Sickle cell disease and other causes

Sickle cell anemia variants, structural variants of the alpha or beta globin chains (rarely), cytoskeletal defects, and enzymopathies may be associated with an elevated MCV, but these conditions are all accompanied by distinctive clinical findings, such as jaundice, or lab abnormalities such as unconjugated hyperbilirubinemia or elevated levels of lactate dehydrogenase (with isoenzymes 1 and 2 elevated, and isoenzymes 4 and 5 decreased). The peripheral blood smear will usually show polychromasia and may give clues to the cause of the reticulocytosis.

■ DRUGS AND HERBAL REMEDIES

Certain drugs may interfere with DNA metabolism and can cause an elevated MCV, including antimetabolites (eg, azathioprine, methotrexate), antiretroviral agents, and alkylating agents such as cyclophosphamide. Some herbal remedies may also cause red blood cell anomalies. For example, some herbal preparations contain arsenic, which interferes with DNA metabolism.

■ FALSELY ELEVATED MCV

False elevations of the MCV can be caused by other conditions. Certain red blood cell agglutination syndromes such as cold agglutinins can falsely elevate the MCV because automated machines may interpret agglutinated red blood cells as single, large red blood cells.

Rouleaux formation, as seen in paraproteinemias, may also falsely raise the MCV. Some patients with Waldenström macroglobulinemia may feel entirely well and have negligible anemia but have elevated serum viscosity, elevated IgM, and significant rouleaux.

■ MALABSORPTIVE CONDITIONS

Mild changes in red cell number or size may be the presenting symptom of celiac disease, which causes micronutrient malabsorption that can produce folate deficiency.⁶

These changes may also herald other malabsorptive states, such as lymphoma of the gut, amyloid infiltration of the gut, lymphangiectasia, or Whipple disease, any of which may cause folate malabsorption.

■ TRAUMA TO RED CELLS

Trauma to red cells can lead to macrocytosis. One type of patient at risk of this problem is the long-distance runner, who constantly injures red cells in the microcirculation of the foot.⁷

Occasionally, elevated MCV is associated with abnormally seated prosthetic heart valves and regurgitant jets. After aortic valve surgery and mitral valve repair, one can see schistocytes on the peripheral blood smear, along with polychromasia and reticulocytosis. ■

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