Macrocytosis As An Indicator Of Human Disease

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Abstract: **Adult patients with macrocytosis, defined as a mean corpuscular volume (MCV) greater than 100 femtoliters, were studied to assess the importance of an elevated MCV. After eliminating pregnant and postpartum patients and patients receiving medications known to cause macrocytosis (e.g., phenytoin, zidovudine, and chemotherapeutic agents), 80 patients were identified and studied. Sixty-seven diagnoses were made in 56 patients. These diagnoses were, in descending order: alcoholism, hematological disorders, habitual drinking, B_{12} deficiency, chronic liver disease, folic acid deficiency, hypothyroidism, anorexia nervosa, and reticulocytosis. While an elevated MCV is neither sensitive nor specific for any one disease state, an elevated MCV should raise suspicions of underlying pathology. (J Am Bd Fam Pract 1989; 2:252-6.)**

With the advent of the automatic cell counter, physicians have had available to them a number of red-cell indices, including the mean corpuscular volume (MCV). An elevated MCV (macrocytosis) can be seen in a variety of medical conditions and can be caused by several types of drugs.[1-5] Failure to attend to elevated MCV, even when anemia is not present, might be detrimental to the patient. This study was undertaken to see whether investigating unexpected macrocytosis is clinically useful and rewarding.

Causes of Macrocytosis

Macrocytosis can be seen when normal maturation of the red-cell nucleus is inhibited as in folic acid or cobalamin (B_{12}) deficiency (Table 1). Medications that interfere with folic acid utilization (e.g., phenytoin and methotrexate [commonly] and the sulfa derivatives and phenobarbital [less commonly]) can also result in macrocytosis.[5] Direct inhibition of nuclear maturation by anticancer chemotherapeutic agents and zidovudine (AZT) can produce an elevated MCV. A variety of congenital disorders also show inhibited nuclear maturation. Chronic liver disease, presumably by interfering with the synthesis of the red-cell membrane, can give rise to macrocytes that often appear as target cells. Hypothyroidism, too, may cause macrocytosis, sometimes with anemia, although the mechanism is poorly understood. Macrocytosis has been observed in populations of patients with chronic obstructive pulmonary disease (COPD), but it is not known whether the lung disease itself or some related problem causes the MCV to rise.[6,7]

For a variety of reasons, alcohol abuse and macrocytosis are linked. Alcohol can act as a direct bone marrow toxin and produce macrocytes that are often "thin" and have a reduced mean cell hemoglobin (MCH). Alcoholics may also develop folic acid deficiency from an improper diet. A lack of pyridoxine may result in pyridoxine-responsive sideroblastic anemia, which can be seen in as many as one-third of hospitalized alcoholics. Finally, alcohol can interfere with cobalamin absorption.[8,9]

An elevated MCV occurs in hematological disorders, particularly myelodysplastic, preleukemic, and leukemic syndromes. Myelodysplasia, a heterogeneous group of disorders often observed in the elderly, results in disordered bone marrow production with an anemia refractory to most treatments. Pyridoxine-resistant sideroblastic anemia is one type of myelodysplasia. These disorders may be associated with macrocytosis, although the red cells can be normal, or even reduced, in size.[10]

Because reticulocytes are larger than mature red cells, any process that increases the relative proportion of reticulocytes to mature red cells (e.g., hemolytic anemia) can cause a rise in the MCV, although the effect is usually transient.

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Artifactual macrocytosis must be considered. Osmotic forces can draw free water into erythrocytes; this happens when erythrocytes from patients with longstanding hypernatremia or hyperglycemia are mixed with the diluent used in automatic cell counters.[11,12] In hemagglutination, automatic cell counters read such clumps as single cells and report falsely high MCVs. Extremely high values (more than 140 femtoliters) are often due to this process.[13]

Other miscellaneous conditions associated with macrocytosis are presented also in Table 1.

Table 1. Causes of Macrocytosis.

Increased number of reticulocytes
Hemorrhage
Hemolytic anemia
Vitamin deficiency
B_{12} deficiency
Pernicious anemia
Postgastrectomy
Malabsorption syndromes (e.g., sprue)
Fish tapeworm infestation
Dietary insufficiency (strict vegetarians)
Familial malabsorption
Isolated inability to absorb B_{12} from food
Folic acid deficiency
Increased demands (e.g., pregnancy, exfoliative dermatitis)
Dietary insufficiency
Medications
Folic acid antagonism
Phenytoin and mephenytoin
Methotrexate
Pentamidine
Primidone
Pyrimethamine
Triamterene
Trimethoprim
Trimethoprim-sulfamethoxazole
Trimetrexate
Chemotherapeutic agents
Zidovudine
Methyldopa (by induction of hemolytic anemia)
Artifactual
Hypernatremia
Hyperglycemia
Cold agglutinin disease
Miscellaneous
Alcoholism
Neonatal macrocytosis
Hypothyroidism
Chronic liver disease
Down syndrome
Postsplenectomy
Chronic obstructive pulmonary disease
Preleukemic and myelodysplastic syndromes
Inherited disorders of DNA synthesis
Hereditary orotic aciduria
Lesch-Nyhan syndrome
Methylmalonic aciduria
Formiminotransferase deficiency
Dihydrofolate reductase deficiency
Abnormal or deficient transcobalamin II

Methods

Inpatient and outpatient laboratory work of a 4-physician family practice was periodically screened during a 45-month period for macrocytosis (defined as an MCV >100 fL). A single value greater than 100 fL was sufficient for inclusion in the study. The charts of these patients were then reviewed for problems that could be related to macrocytosis. Patients on medications known to induce macrocytosis, as well as pediatric and obstetrical patients, were deleted from the study group.

When possible, patients were contacted and asked to have B_{12} and folic acid levels done. Because serum folate levels change rapidly with short-term variations in dietary intake, red-cell folate levels were used when practical to indicate the true deficiency more accurately.

Patients who admitted to alcohol consumption were asked to fill out a questionnaire that incorporated questions from the Michigan Alcohol Screening Test (MAST). Patients were asked to estimate their daily alcohol consumption, and on the basis of their answers, they were divided into one of three groups: social drinkers, habitual drinkers who did not meet the criteria for alcoholism, and active alcoholics. They were considered active alcoholics if they met the criteria of the American Medical Association's task force on standardization of drug use terminology ("Alcohol abuse: use of ethyl alcohol in a quantity and with a frequency that causes the individual significant physiological, psychological or sociological impairment")[14] or had MAST scores of five or more and were currently drinking. Patients who

Table 2. Criteria for Habitual Drinking.

Sex	Weight	Criterion*
Women	≤ 100 pounds	2 drinks daily
Women	> 100 pounds	> 2 drinks daily
Men	≤ 140 pounds	3 drinks daily
Men	> 140 pounds	> 3 drinks daily

*One drink consists of 12 ounces of regular beer, 1 ounce of liquor, 4 ounces of wine, or their equivalents.

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were not actively drinking at the time of the study were believed not to have alcohol-induced macrocytosis and were not included among the active alcoholics. Habitual drinking was defined on the basis of weight and sex (Table 2).

Because smokers often have other behaviors that are detrimental to their health, a smoking history was obtained to see if alcohol abuse was more frequent in those patients who had macrocytosis and were actively smoking.

Additional laboratory studies were done (e.g., thyroid testing, bone marrow biopsies) as indicated to assist in diagnosis. Bone marrow biopsies were not performed on patients who felt well and did not have a significant anemia.

Results

Unexpected macrocytosis occurred fairly frequently during the course of the study. Eighty patients met the study's criteria. Forty-five were men (aged 28–86 years, median = 61); 35 were women (aged 18–95 years, median = 67.5). The majority were white; 3 were Hispanic, and 1 was black. The study group mirrored the demographics of the practice.

In the 80 patients, a relevant diagnosis was made in 56 (Table 3). These patients had a total of 67 conditions that could cause an elevated MCV. Of the 67 diagnoses made, 38 were discovered in the course of evaluating the macrocytosis.

Table 3. Diagnoses of 80 Patients with Unexpected Macrocytosis (Note: Several Patients Had More Than One Diagnosis).

Unknown – 22
Alcohol related – 29
Alcoholics (20)
Habitual drinkers (9)
Hematological – 9
Leukemia (3)
Myelodysplasia (2)
Idiopathic pancytopenia (1)
Preleukemia (1)
Polycythemia vera (1)
Thrombocytopenic purpura (1)
Chronic liver disease – 7
B_{12} deficiency – 8
Pernicious anemia (6)
Malabsorption (1)
Unknown (1)
Folic acid deficiency – 5
Hypothyroidism – 5
Anorexia nervosa – 2
Elevated reticulocytosis – 2

The level of macrocytosis was only somewhat related to the likelihood of finding pathology. Fifty-nine patients had an MCV of 101–105 fL, and 41 of these had some disease process that could account for the macrocytosis. In the 11 patients whose MCVs were between 106 and 110, 7 were diagnosed, and in the 10 patients whose MCV was greater than 110, 8 had at least one disease present.

Alcoholism and habitual drinking together accounted for 29 of the diagnoses. Drinking behavior of 15 patients was unknown to the primary care doctor. Ten percent of the nonsmokers had an alcohol-related problem compared with 63 percent of the smokers.

B_{12} and folic acid levels were measured in 74 patients, and vitamin deficiencies were found in 13. Eight had low B_{12} levels, and 5 had low folic acid levels. Three more patients had borderline levels of B_{12}, and one had a borderline red-cell folate level. Six patients with a low B_{12} level had pernicious anemia, one had malabsorption secondary to a jejunal-colic fistula, and one refused further work-up. Only 2 patients with B_{12} deficiency were anemic when diagnosed.

Of the patients with folic acid deficiency, one had anorexia nervosa that was quite unexpected until work-up disclosed the low folate level and further investigation was done. A second patient with anorexia nervosa most likely had folic acid deficiency but had to be transported to an inpatient psychiatric facility before testing could be done. Another patient with unexpected folate deficiency had achalsia when studied further.

Nine patients had hematological diseases, including 3 with leukemia, one with preleukemic changes, 2 with myelodysplastic syndrome, one with polycythemia vera, one with thrombocytopenic purpura, and one with idiopathic pancytopenia. The last 2 patients were also alcoholics.

Seven patients had chronic liver disease, but these were not new diagnoses. Hypothyroidism was found in 5 patients, although thyroid testing was done only when clinically indicated. Three of the 5 diagnoses were unexpected because the patients were clinically euthyroid. In fact, one patient had thyroid studies done because of difficulty in controlling hypertension, and another because of difficulties controlling cardiac arrhythmias. Two of the 5 patients with hypothyroidism had mild anemia; both macrocytosis and

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anemia resolved after treatment with thyroid hormone.

Six patients had clinically important lung disease. Each, however, had at least one other disease process that could explain the macrocytosis.

Finally, two patients had reticulocytosis; one as a response to an acute hemorrhage (this patient was also folate deficient). The second, on lithium therapy, refused further work-up.

Discussion

All told, an explanation for macrocytosis was found in 70 percent of the study patients. Perhaps more important is the fact that 57 percent of the diagnoses were previously unknown to the primary doctor, thus establishing the importance of investigating an elevated MCV. Even minimally elevated MCVs had a high likelihood of being associated with some disease state.

In designing this study, a careful attempt was made to identify problem drinkers. It was clear that there were a number of patients with a fairly high, regular alcohol intake who did not meet the established criteria for alcohol abuse. A separate category, habitual drinking, was used to describe them. Such a subset of patients may be important to identify because an elevated alcohol intake is thought to be a risk factor in such conditions as hypertension, osteoporosis, diabetes mellitus, and cerebrovascular disease.

Alcoholism and habitual drinking together accounted for 36 percent of the patients with macrocytosis. This may actually represent an underestimation, and, indeed, at least 3 patients who did not admit to a high intake were strongly suspected to be problem drinkers. Unfortunately, macrocytosis is not a reliable screening tool for alcohol abuse, because many alcoholics do not have an elevated MCV, which may be due to coexisting conditions such as iron deficiency or thalassemia minor. An elevated MCV is useful, though, for alerting the physician that alcohol abuse may be a problem.[15,16]

For example, 2 patients who were initially thought to have B_{12} deficiency alone were found to be very heavy drinkers when they were questioned about their alcohol intake. Another, who initially admitted to only two drinks a day, when questioned more closely, admitted to drinking two 8-ounce glasses of straight Scotch whisky daily.

Vitamin deficiencies were found in a moderate number (16 percent) of the patients. One patient with pernicious anemia had an elevated MCV (120 fL), with mild anemia, when hospitalized 2 years previously; work-up then would have prevented the profound anemia that developed and obviated the need for a second hospitalization. Apparently, ignoring an elevated MCV is not unusual; several studies have been reported where an opportunity to make an early diagnosis of pernicious anemia was missed.[17,18] (In fact, abnormally low MCVs have also been frequently overlooked.[19,20]) As in alcohol abuse, pernicious anemia may be present without macrocytosis because of concomitant medical problems.[21]

Although prior studies have noted an association between chronic obstructive pulmonary disease (COPD) and macrocytosis, this study did not identify a single patient who had macrocytosis based solely on the presence of COPD. Instead, the macrocytosis was most likely explained by a high alcohol intake or a vitamin deficiency. The association between smoking and macrocytosis as an indicator of greater than normal alcohol use has been noted elsewhere, at least in men.[16]

Limitations

This study did not include patients who were receiving drugs known to cause macrocytosis. This does not mean that these patients may not have other causes for their macrocytosis. For example, patients with the acquired immune deficiency syndrome may be taking zidovudine, trimetrexate, or pyrimethamine, any one of which could cause macrocytosis. However, it is becoming increasingly obvious that AIDS patients may have significant deficiencies in both folic acid and cobalamin.[22,23]

By design, a single episode of macrocytosis was sufficient for inclusion in the study; whether persistent macrocytosis may be a better screen remains to be investigated. Red-cell distribution widths (RDWs) were not available. Conceivably, patients with borderline elevations of their mean corpuscular volumes who also have abnormal RDWs may benefit from further revaluation.

Summary

An elevated MCV is neither sensitive nor specific for any one condition, but, like an elevated

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sedimentation rate, an elevated MCV is often indicative of an underlying problem. Because the MCV is a routine measurement on most automated cell counters, it has the added advantage of being extremely economical.

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