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How do you evaluate macrocytosis without anemia?

Evidence-based answer

Start with a detailed history, paying particular attention to medications and alcohol use (strength of recommendation [SOR]: **B**, prospective cohort studies). Blood testing can include a peripheral smear, evaluation for vitamin deficiencies (especially B_{12} deficiency), and liver function tests (SOR: **B**, inconsistent prospective cohort studies). Thyroid testing may be useful for older patients (SOR: **B**, prospective study). Reticulocyte count and bone marrow evaluation, although important to rule out hemolysis and myelodysplastic changes, may not be necessary for patients with isolated macrocytosis without anemia (SOR: **B**, prospective cohort studies). In unexplained macrocytosis, bone marrow evaluation may show early marrow changes, particularly in the elderly (SOR: **B**, prospective cohort study).

Clinical commentary

When the cause isn't clear, think alcohol

Macrocytosis without anemia is not that rare, in my experience, and the cause usually becomes clear with a medication history and a few laboratory tests, such as vitamin B_{12} studies and thyrotropin. When I see a patient with macrocytosis without an obvious cause, I think of alcohol use.

Sometimes the only hint of a larger underlying problem is overlooked or passed off as a minor laboratory variation amid other normal results. On more than one occasion, I have been able to unmask an occult drinking problem by paying attention to this parameter on the complete blood count. This Clinical Inquiry is a good lesson in understanding the implications of all of the parameters of a CBC, not focusing just on the traditional white blood cell count, hematocrit and hemoglobin, and platelet counts.

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When I see a patient with macrocytosis without an obvious cause, I think of alcohol use

Evidence summary

Significant macrocytosis is usually defined as a mean corpuscular volume greater than 99 femtoliters (fL). The prevalence of macrocytosis (with or without anemia) ranges from 1.7% to 5.0%.[1-4] As many as 60% to 80% of primary care patients may not have anemia.[3,4]

Because no study has looked specifically at evaluating macrocytosis without anemia, extrapolation from studies of all presentations of macrocytosis (with and without anemia) must help guide evaluation.[1,3,5-7] The causes of macrocytosis vary depending on the population studied (**TABLE**). In primary care, alcohol use and vitamin deficiency are common causes. Even after evaluation, approximately 10% of cases remain unexplained.[3]

Clues in the history, physical exam, and lab results

A history focusing specifically on alcohol use and medications—especially chemotherapeutics, antiretroviral drugs, and antiseizure medications—can provide important clues to the cause of macrocytosis. During the physical examination, look for signs consistent with chronic liver disease.

Laboratory studies can help identify vitamin deficiencies, liver disease, and thyroid disease. A normal serum B_{12} level may not rule out a true B_{12} deficiency, but normal levels of the metabolites methylmalonic acid and homocysteine do essentially rule it out.[8] In this era of folic acid fortification, the utility of the serum folate level is uncertain. Several studies suggest empiric treatment with folic acid instead of testing for a deficiency when B_{12} deficiency has been ruled out.[7,9]

Liver disease—which may be confounded by alcohol abuse, medications, or cancer—is a common cause of macrocytosis.[5] Hypothyroidism is rarely a cause, but may be more prevalent in the elderly.[10]

What these 2 tests may, or may not, tell you

Although several authorities recommend a peripheral smear and reticulocyte count to help evaluate macrocytic anemia, no specific recommendations exist for these tests in the absence of anemia. A peripheral smear can detect megaloblastic changes typical of B_{12} and folate deficiency and other marrow disorders, especially myelodysplastic changes. Peripheral smear findings and reticulocytosis can also show evidence of hemolysis. However, megaloblastic changes and marrow-related changes on peripheral smear are typically seen with anemia.

In 2 prospective studies of primary care patients, 1 reported little diagnostic value for the peripheral smear,[1] and the other found that reticulocytosis rarely caused macrocytosis.[5] A prospective study of 300 hospitalized patients with macrocytosis found that 100% of marrow disorders and hemolysis that caused macrocytosis also caused an associated anemia.[7] A retrospective chart review of 113 cases of macrocytosis in outpatients found that general practitioners often didn't order a peripheral smear and reticulocyte count to complete their diagnostic workups.[4]

Bone marrow biopsy may reveal dysplastic changes, but not a Dx

A prospective study of the utility of bone marrow biopsy in 124 elderly patients with macrocytosis found that as many

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Although hypothyroidism rarely causes macrocytosis, it may be more prevalent in the elderly

TABLE

Causes of macrocytosis: What prospective studies show

CAUSE	PERCENT OF PATIENTS BY STUDY				
	DAVIDSON[6] (N=200)	BREEDVELD[1] (N=70)	KEENAN[5] (N=80)	SAVAGE[7] (N=300)	MAHMOUD[10] (N=124)
Alcohol	18	27	36	26	14
Vitamin deficiency	13	39 (6% had both deficiencies)	16	6	24
B_{12}	8	23	10	5	12
Folate	5	10	6	1	12
Medications	30	1	—*	37	2
Liver disease	16	3	9	6	2
Hematologic disease	15	19	14	14	20
Malignancy/ premalignancy	15	13	11	6	20
Reticulocytosis	0	6	3	8	—†
Hypothyroidism	—†	3	6	1	12
Unexplained	23	9	28	7	19

* Excluded patients on cytotoxic and chemotherapeutic medications
† Not evaluated.

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As many as 60% of elderly patients with macrocytosis were diagnosed by blood test alone

as 60% were diagnosed by blood tests alone. All the remaining patients with unexplained macrocytosis underwent bone marrow biopsy, which showed early dysplastic changes in 39%, but did not provide a diagnosis in nearly 50%. Twelve percent were found to have myelodysplastic syndrome, but they had a mean hemoglobin of 8.5 g/dL.[10]

Recommendations

We were unable to find published guidelines for the evaluation of macrocytosis without anemia by the American Society of Hematology, the British Committee for Standards in Haematology, or in an authoritative hematology text.[11] ■

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