Equivocal Anemia in the Elderly

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Anemia in the elderly is difficult to define, but it is generally recommended that normal red blood cell values established for the general population be applied to the elderly based on studies of healthy, ambulatory, elderly persons.[1] Many elderly persons, however, have borderline values, with concentrations at or below the lower end of the normal hemoglobin or hematocrit range, that overlap with values that signify disease. According to the article "Anemia in the Elderly: A Survey of Physicians' Approaches to Diagnosis and Workup" by Daly and Sobal[2] in this issue, a significant number of practicing physicians tend to disregard the relevance of laboratory results in this gray zone. The clinician, believing that the borderline value either is an age-related change or is caused by an uncorrectable covert chronic disease, is reluctant to subject the majority of patients to a potentially unproductive investigational workup. Furthermore, as shown by Daly and Sobal, not all clinicians will investigate a definite mild anemia. In general, a decision not to work up a mild anemia may be a conscious decision to limit care for severely impaired patients or, in the case of apparently healthy ambulatory older people, the acceptance that most cases that are investigated are unexplained and nonresponsive to therapy.

Arguments have even been promulgated to lower hematologic values as a new norm for the elderly.[3] Doing so would eliminate investigative workups for patients thought to have a lower risk of underlying pathology. But this approach includes both normal asymptomatic older people and those who are truly anemic. It is considered less risky to use such an approach with healthy ambulatory old people. There is a hazard of overlooking a benign lesion or even a treatable malignancy, usually of the gastrointestinal tract, or in frail elderly impaired patients of ignoring that even mild anemia may have detrimental effects. In contrast to young adults, who may not develop symptoms with mild anemia or show beneficial results with a rise of their hemoglobin level, small improvements may have profound effects on the functional capability of older people.

Young adults do not develop significant cardiorespiratory or other functional symptoms until the hemoglobin level is below 80 g/L (8.0 g/dL). In contrast, because of the decline in functional reserve of most organs of the elderly, a mild to moderate anemia can cause confusion or worsen a dementia, precipitate or intensify congestive heart failure or anginal attacks, cause syncope and falls from postural hypotension, aggravate functional disability and fatigue in arthritis, parkinsonism, or stroke, and dampen motivation for rehabilitative measures.

Although anemia is not due to the aging process as such, the term *anemia of senescence* has been applied to anemia in the elderly that remains unexplained after standard laboratory evaluation. Many body functions show a progressive decline with aging, and it has been suggested that the function of the bone marrow is similarly reduced with aging. In most organs, functional capacity, especially reserve capability, declines at variable rates. This reduced capacity prevents optimal function under the stress of increased demands. A similar phenomenon seems to occur with bone marrow function. With aging, both animal and human studies suggest decreased bone marrow hematopoietic function.[4] Evidence suggests that impaired production of hematopoietic growth factors is a likely cause (M.A. Lee, G.A. Segal, G.C. Bagby, February 1989, unpublished data). The basal or steady state production of blood cells remains adequate in most elderly individuals, however, and anemia cannot be attributed to aging alone. It is often difficult in studying older people to separate the effects of inapparent disease, medications, nutritional deficiencies, and environmental toxins from the aging process itself.

Evaluation of the elderly patient with anemia involves a complete blood count including red blood cell indices, a reticulocyte index, and examination of the peripheral blood smear. A stool should be examined for occult blood. Annual testing of stools for occult blood for all patients aged over 50 years to detect colorectal lesions is recommended regardless of the presence of anemia. Mild anemias usually do not show the classic morphological changes of erythrocytes, and the red blood cell indices are normal. With iron deficiency, the initial event is a deple-

Submitted March 6, 1989.

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tion of bone marrow iron stores, which can be detected by measuring a serum ferritin level. Sequential changes follow in the serum iron, total iron-binding capacity (TIBC), and finally the red blood cell morphology.

Anemia may be absent with vitamin B_{12} deficiency, especially in patients with neurological lesions.[5,6] Similarly, macrocytosis may be absent in about one third of patients diagnosed with pernicious[6] anemia, especially when complicated by a coexisting iron deficiency, thalassemia, or with predominant neurological involvement.

In addition to the dilemma in defining hematologic criteria for anemia, there are aging, disease, and lifestyle influences on interpretation of other laboratory values in the elderly. A low serum iron associated with a high transferrin or TIBC produces a low percentage of iron saturation of transferrin characteristic of iron deficiency in both young and old patients. These guidelines, however, are modified in some elderly patients. The serum iron decreases progressively with age, especially in the presence of neoplasm, infection, or inflammation, even when bone marrow iron stores are normal. Undetected chronic disease rather than age itself frequently accounts for these changes. Serum transferrin is often decreased in the elderly, presumably as a result of coexisting chronic disease or protein-calorie malnutrition.[7] As a consequence, both the serum iron and transferrin values are decreased, and the percentage of saturation of transferrin may be greater than 15% the value below which iron deficiency is considered likely in younger individuals. Therefore, the serum iron and TIBC are compromised in frail elderly patients and may be misleading.

A bone marrow study is unnecessary for the study of iron stores, since serum ferritin reflects storage iron. Bone marrow iron increases with age, and an increase in serum ferritin is especially prominent in postmenopausal women. A serum ferritin value, however, must be interpreted in the light of coexistent disorders. In an uncomplicated patient a serum ferritin below 12 μg/L (12 ng/mL) indicates iron deficiency. In a patient with an anemia of chronic disease (ACD), a serum ferritin below 25 μg/L (25 ng/mL) is highly predictive of an associated iron deficiency and merits a trial of iron therapy. Patients with chronic inflammatory disease, liver disease, or malignancy show serum ferritin values over 50 μg/L (50 ng/mL), and values below this level are consistent with iron deficiency.

With newly revised, sensitive radioassay techniques, low levels of serum B_{12} values are found frequently. The evaluation for vitamin B_{12} (cobalamin) deficiency should be considered with values below 70 pmol/L (100 pg/mL), but it is becoming evident that using this low serum vitamin B_{12} value will miss some patients with deficiencies.[6,8] On the other hand, in a normal elderly person, a low serum B_{12} level may not represent a deficiency but may be due to decreased cobalamin binding sites on transcobalamin II, which is the plasma protein carrier responsible for transporting B_{12} to the tissues.[9]

A serum vitamin B_{12} level below 150 pmol/L (200 pg/mL) in an anemic patient with macrocytosis, hypersegmented polymorphonuclear leukocytes, peripheral neuropathy, or dementia is consistent with a diagnosis of vitamin B_{12} deficiency even if the Schilling test is normal. While an abnormal urinary excretion of radiolabeled B_{12} (Schilling test) is confirmatory, it may be normal in an early stage of vitamin B_{12} deficiency anemia. The patient may be able to absorb free (unbound) vitamin B_{12} used in the classic Schilling test but may have lost the ability to split vitamin B_{12} from its peptide bonds and therefore be unable to absorb vitamin B_{12} from food.[10] Other measures of B_{12} tissue deficiency used in research units, such as elevated serum or urinary methylmalonic acid or abnormal bone marrow deoxyuridine suppression tests, are helpful if available.

While serum vitamin B_{12} levels are helpful in differentiating anemias, they can also be useful in studying nonanemic patients with neurological lesions, particularly dementias. In searching for correctable causes of dementia, a low serum vitamin B_{12} level is sometimes uncovered, allowing for subsequent reversal of the cognitive disorder with treatment. This gratifying response is seldom achieved, however. Recently two studies[11,12] have reported low serum B_{12} levels in 30% of patients with primary degenerative dementia, suggesting a link that does not exist in other forms of dementia. Other classic hematological changes suggestive of B_{12} deficiency were infrequently found, and the meaning of the low serum B_{12} levels and a relationship to Alzheimer-type dementia needs further clarification.

As Daly and Sobal suggest, lumping unexplained anemias of the elderly into a package called anemia of senescence ignores the cause(s). Further clarification is needed to determine whether occult underlying disease is responsible for the diagnosis of either anemia of senescence or the anemia of chronic disease in some elderly patients. Both of these diagnoses are overused in older people with unexplained anemia. Before establishing a new set of hematologic norms for the elderly, more evidence is needed on healthy ambulatory elderly persons.

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