Chapter 2

Diagnosis of Megaloblastic Anemia

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The recognition of megaloblastic anemia rests on clinical and hematologic features that have been known for many years. The diagnostic tools, however, have become more refined and reliable, thus allowing specific diagnosis to be made more accurately and in more subtle kinds of disorders than before.

In order to take full advantage of these tools, two diagnostic principles must be followed. First, it is necessary in all cases to establish as firmly as possible the specific vitamin abnormality responsible for the megaloblastic anemia. In the vast majority of cases, this is deficiency of either folic acid or cobalamin (vitamin B12), or sometimes of both vitamins. The second principle is that it is as important to diagnose the underlying disorder that produced the deficiency as it is to identify the vitamin deficiency.

This chapter reviews the diagnostic aspects of megaloblastic anemia itself, and then the diagnostic details of the two principles mentioned.

Megaloblastic Anemia

Whether the characteristic megaloblastic anemia is directly responsible for the patient’s seeking medical attention or not, it is usually the feature that prompts consideration of the diagnosis. Very mild or partially masked abnormalities, however, often make the diagnostic task difficult.

Although most patients are anemic, and many have pancytopenia, sometimes anemia is absent or very mild. Indeed, 19-25% of patients with megaloblastosis have normal hemoglobin values [37]. The mechanism of anemia is one of ineffective erythropoiesis, with a hemolytic component in many cases. Therefore, evidence of increased erythroid destruction, such as indirect hyperbilirubinemia and elevated lactate dehydrogenase levels, is common; however, it is not invariable [27].

Macrocytosis is a major clue to the existence of megaloblastic anemia. Due to the widespread use of electronic cell counters and the fact that development of macrocytosis precedes the development of anemia [56], attention to the mean corpuscular volume (MCV) is very helpful diagnostically [16]. Elevated MCV is the most accessible marker for megaloblastic anemia. However, it has limitations. Table 1 lists the conditions in which macrocytosis may occur. Most surveys suggest that the more striking the macrocytosis, the greater is the likelihood that megaloblastic anemia is responsible for it [75]. However, numerous excep-
Table 1. Causes of macrocytosis

1. Megaloblastic anemia
2. Drugs
   - Alcohol
   - Chemotherapeutic and immunosuppressive agents (e.g., azathioprine)
3. Hematological disorders
   - Aplastic anemia
   - Pure red cell aplasia
   - Myeloproliferative disease
   - Leukemia
   - Multiple myeloma
   - Refractory anemia
   - 5q- syndrome
   - Hemolytic anemia
   - Hereditary hydrocytosis
4. Nonhematological diseases
   - Liver disease (usually, but not invariably, alcoholic)
   - Hypothyroidism
5. Physiological
   - MCV is normally elevated in the first 4 weeks of life
6. Idiopathic
   - Pregnancy
   - Old age
   - Chronic lung disease, smoking
   - Cancer
7. Artifact
   - Cold agglutinins
   - Severe hyperglycemia
   - Hyponatremia
   - Stored blood

* Higher MCV levels have been observed in pregnancy, old age, smoking, and cancer, but the mechanism is unknown, and the possibility of subtle megaloblastosis as the explanation has not been entirely excluded.

...tions occur, and reliance on such a rule can never substitute for careful examination of the hematologic and clinical picture. Furthermore, it is not unusual for megaloblastic anemia to coexist with one of the other causes of macrocytosis, particularly with chronic alcoholism.

Despite the great usefulness of the MCV, macrocytosis is not invariably seen in megaloblastic anemia. Normal or even low MCV may result when disorders that produce microcytosis coexist with megaloblastic anemia [53, 97]. Normal MCV has been said to occur in about 10% of patients with megaloblastic anemia [37, 88]. However, recent reports have noted an incidence of 33%-40% in patients with pernicious anemia [18a, 23, 98]. The explanation for this higher incidence may lie in the high proportion of black patients in these series, but the earlier recognition of disease with the widespread use of more sensitive cobalamin assays may also have contributed to this startling incidence. In many cases, the normal MCV remains unexplained.

It is also useful to remember that children have lower MCV than adults. “Microcytosis” is the norm from the age of 4-6 months to the age of 10 years or so...