Megaloblastic Anemias
Nutritional and Other Causes

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KEYWORDS

• Anemia • Megaloblastic • Vitamin B_{12} • Folate • Pernicious anemia
• Methylmalonic acid • Homocysteine • Transcobalamin

KEY POINTS

- Vitamin B_{12} and folate deficiencies are the most important causes of megaloblastic anemia.
- The main cause of vitamin B_{12} deficiency that results in megaloblastic anemia is pernicious anemia caused by autoimmune destruction of gastric parietal cells.
- The prevalence of folate deficiency has decreased because of widespread food folate fortification, but it still occurs among the poor, elderly, and alcoholics, particularly in countries that do not fortify the diet. It can also result from malabsorption or increased cell turnover and increased demand.
- Nuclear-cytoplasmic asynchrony from the ineffective DNA synthesis causes megaloblastic changes in the bone marrow with resulting anemia and cytopenias.

MEGALOBLASTIC ANEMIAS: NUTRITIONAL AND OTHER CAUSES
Introduction

Ineffective DNA synthesis in hematopoietic precursor cells is the primary mechanism that leads to megaloblastic anemia. The most frequent causes of megaloblastic anemia are deficiencies of either vitamin B_{12} or folate within a long list that includes deficiency of other micronutrients, congenital disorders, myelodysplastic syndromes, and acquired DNA synthesis defects as seen in the settings of chemotherapy (**Box 1**).[1] The ineffective hematopoiesis resulting from the asynchrony between nuclear and cytoplasmic development is most evident on Wright-Giemsa–stained bone marrow aspirate smears. Megaloblastic erythroid precursors are larger than normal and their nuclei are larger and appear immature with granular chromatin. During the initial stages of cellular differentiation, the slow condensation of chromatin results in an open sievelike vesicular nucleus. In subsequent stages there is more cytoplasm in

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Box 1
Causes of megaloblastic anemia

Vitamin deficiencies

Deficiency of folate
1. Decreased intake
   a. Nutritional deficiency (elderly, alcoholics, poverty)
   b. Diet induced: goat's milk, synthetic diets
   c. Infants with prematurity
   d. Hyperalimentation
2. Decreased absorption
   a. Celiac disease and tropical sprue
3. Increased demand
   a. Pregnancy
   b. Puberty
   c. Chronic hemolytic anemia
   d. Exfoliative dermatitis
   e. Hemodialysis

Deficiency of vitamin B_{12}
1. Impaired absorption
   a. Pernicious anemia
   b. After gastrectomy or ileal resection
   c. Zollinger-Ellison syndrome
   d. Blind loop syndrome
   e. Fish tapeworm infestation
   f. Pancreatic insufficiency
2. Decreased intake
   a. Vegans
   b. Vegetarians

Other causes

1. Drugs (eg, antibiotics, anticancer agent, anticonvulsants and oral contraceptives)
2. Inborn errors of metabolism
3. Acute megaloblastic anemia
   a. Nitrous oxide exposure
   b. Acute illness
4. Idiopathic (congenital dyserythropoietic anemia, erythroleukemia, and refractory megaloblastic anemia)
5. Thiamine-responsive megaloblastic anemia

the megaloblastic erythroid precursors relative to the size of the nucleus. The granulocytic precursors also show nuclear-cytoplasmic dyssynchrony with the development of so-called giant metamyelocytes and bands, which have a characteristic horseshoe-shaped nucleus and open chromatin. The development of megakaryocytes is also affected, as reflected by abnormal large polylobated megaloblastic megakaryocytes with a lack of cytoplasmic granules. Corresponding changes in the blood smear include anemia with oval macrocytes, anisocytosis, poikilocytosis, leukopenia with hypersegmented polymorphonuclear cells, and thrombocytopenia.

Pathogenesis of Megaloblastic Anemia

Deficiencies of folate and vitamin B_{12} are the leading causes of megaloblastic anemia worldwide. In the era of food folic acid fortification, there is a decreasing trend of folate deficiency prevalence in most developed countries. Classically, in megaloblastosis,