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## Letter to Editor

## A diagnostic and therapeutic conflict with masked megaloblastosis

Iffat Jamal <sup>1,\*</sup><sup>1</sup>Dept. of Hematology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

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Megaloblastosis is a cytomorphological diagnostic sign for megaloblastic anaemia, which is a morphological and functional erythropoiesis abnormality. At all stages of maturity, megaloblasts have various cytomorphological traits that distinguish them from normal erythroid precursor cells (i.e., normoblasts).

Larger cell size and a finely stippled, open lacy pattern of nuclear chromatin are two of them. The cytoplasmic characteristics are less striking, with clear asynchrony between nuclear and cytoplasmic maturation. Addisonian pernicious anaemia was the original prototype of this anaemia, which was first identified in Caucasians as the lone example of megaloblastic anaemia in the nineteenth century. This anaemia was eventually determined to be caused by a shortage of vitamin B12 due to a lack of its required binder stomach intrinsic factor, which resulted in malabsorption of this vitamin.<sup>1</sup>

Lucy Wills was the first to describe two types of megaloblastic anaemia: 'pernicious anaemia of pregnancy' and 'tropical macrocytic anaemia,' both of which were later discovered to be caused by a folate deficit (folic acid).<sup>2,3</sup> Even when stomach intrinsic factor is present, it is not uncommon to see staunch vegetarians on the Indian subcontinent who develop vitamin B12 insufficiency and megaloblastic anaemia (due to religious and societal compulsions, food faddism, or poverty). Vitamin B12 and folate insufficiency is a common cause of megaloblastic

anaemia, which can be caused by a variety of factors including low dietary intake, malabsorption, increased need, usage, and excretion.<sup>4</sup> Erythroid precursor cells in the bone marrow of individuals with myelodysplastic syndrome and erythroleukemia can undergo cytomorphological alterations that are comparable to megaloblastosis; however, these latter disorders are rather rare, and the nature of these 'megaloblastic' changes is unknown.

While vitamin-B12 and folate-deficient megaloblastic anemias can be successfully treated by supplementing with the deficient vitamins (folic acid or vitamin B12), 'megaloblastic' alterations associated with myelodysplastic syndrome and erythroleukemia are resistant to these vitamins. Megaloblastic alterations caused by vitamin B12 and folate insufficiency appear to be systemic processes that affect all reproducing cells, not just the erythroid series. In vitamin-B12 and folate deficient megaloblastic anemias, the development of gigantic metamyelocytes and hypersegmented neutrophils is thought to be cytomorphological expressions of these vitamin deficiencies.<sup>1,2</sup>

Masked megaloblastosis is characterised as anaemia caused by a real vitamin B12 or folate deficit that is not accompanied by clinical signs of megaloblastosis in the peripheral blood or bone marrow.<sup>1</sup> This occurs when a concurrent illness, such as iron deficiency anaemia or thalassemia (defective hemoglobinisation), neutralises the ability to create megaloblastic cells. Megaloblastic anaemia with concomitant iron deficiency anaemia is indicated by a

\* Corresponding author.

E-mail address: [iffatjamal111@gmail.com](mailto:iffatjamal111@gmail.com) (I. Jamal).

dimorphic RBC image (macro-ovalocytes plus microcytic hypochromic RBCs) and increased red cell distribution width (RDW) in the presence of normal MCV or MCH.<sup>2</sup> The diagnosis of masked megaloblastosis should prompt further testing to rule out iron deficiency anaemia, chronic illness anaemia, and hemoglobinopathies. Megaloblastosis is unmasked when iron and Vitamin B12/folate deficiencies are treated together.<sup>3</sup>

The only symptom in the CBC values of severe underlying vitamin B12 or folate deficiency—so-called "masked macrocytosis"—is profound anaemia without abnormalities in the Coulter MCV.<sup>5</sup> Masked macrocytosis is not uncommon, affecting up to 9% of patients with megaloblastic anaemia.<sup>6</sup> Patients with pernicious anaemia or dietary folate insufficiency may appear with masked macrocytosis with Coulter MCV values as low as 85 fl. Masked macrocytosis due to pernicious anaemia or folate deficiency is most likely to occur in chronic alcoholics with concurrent deficiencies of both iron and folate, and, as in the present patient, assessing iron stores by serum iron or ferritin levels, iron binding capacity, or examination of a marrow smear stained for iron can all produce normal or misleading results.<sup>4</sup>

Iron stores may appear adequate or increased, but rapid incorporation of iron into new red cells after replacement of the missing vitamin leads to exhaustion of limited available iron and a rapid transition from megaloblastic to iron deficient erythropoiesis, with the development of microcytic hypochromic anaemia.<sup>7,8</sup>

Coexisting folate deficiency or pernicious anaemia and thalassemia is another cause of concealed macrocytosis, notably in blacks, Asians, and other afflicted ethnic groups.<sup>9</sup>

A thorough clinical examination, including a comprehensive review of the CBC, peripheral blood smear, and bone marrow examination, as well as biochemical testing such as iron profile, vitamin B12, and folate assays,

aids in the diagnosis of masked megaloblastosis. It is critical to recognise this illness; otherwise, despite therapeutic trials of vitamin B12/folate alone, anaemia will not be corrected in many cases.<sup>10</sup>


### Conflict of Interest

None.

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### Author biography

Iffat Jamal, Assistant Professor  <https://orcid.org/0000-0001-5574-5569>

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