letter to the Editor

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ASCORBIC ACID DEFICIENCY MAY BE A CAUSE OF REFRACTORINESS TO IRON-THERAPY IN THE TREATMENT OF IRON-DEFICIENCY ANEMIA

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Sir,

we read with interest the comprehensive article by E. Ascari titled *Iron-deficiency anemia resistant to iron therapy* published recently in Haematologica (1993, 78:178-92).

We wish to draw attention to the fact that among the causes underlying *refractoriness* to iron treatment for iron-deficiency anemia the possibility of a concurrent ascorbic acid deficiency has to be kept in mind as well.

We recently[1] observed a 16-year-old boy referred to our Institution for a severe iron-deficiency anemia that was not responding to iron supplementation therapy.

His medical history revealed that his physician had diagnosed iron-deficiency anemia without any detectable cause, and treated him with oral iron supplementation for eight weeks, employing a standard preparation of ferrous salts at a daily dose of 120 mg. After this course of therapy the patient, who showed no improvement, underwent subsequent treatment with intravenous iron: a trivalent iron-gluconate complex at a daily dose of 93 mg for two weeks and then, every three days for another two weeks. However, this further course of iron therapy produced no clinical or hematological response either. For this reason the patient was referred to our Institution.

At the time of admission he still complained of fatigue, weakness, anorexia, mild fever, gingival swelling, petechiae on the surface of both legs and bruises on the left ankle. At physical examination the patient displayed normal growth. No internal organ involvement, including liver, spleen, or gastrointestinal disturbances was revealed.

In addition, no mucosal or visceral (renal, gastrointestinal) bleeding was observed. Likewise, none of the hemostatic tests performed showed abnormalities. Furthermore, instrumentation and laboratory investigations allowed us to exclude any internal organ damage as being responsible for possible occult blood loss. Hemometric analysis confirmed the iron-deficiency anemia (see Table 1), although MCV, iron metabolism parameters and serum ferritin levels were near low normal values. These findings suggested that the iron deficiency anemia present in this patient could be related to a chronic disorder,[2-4] but all of the clinical and laboratory investigations, including serological and cytological autoimmune tests, were negative in this direction. However, further information supplied by the patient's mother led us to discover that for a long time he had refused to eat citrus fruits, fresh vegetables, greens or meat.

Armed with these additional facts, we used appropriate methodology to measure blood levels of some hemoactive vitamins such as B12, folate and vitamin C. Surprisingly we found a significant reduction in serum levels of ascorbate (0.22 mg; n.v. 0.70-1 mg/dL), whereas the values for vit. B12 and folate were within the normal range (560 ng/L and 15 mg/L respectively). RBC folate and vit. B12 levels were also normal. No detectable amount of ascorbic acid was found in WBC. Bone marrow showed no significant changes.

At this point, given the *nutritional deficient status* of the patient, a diagnosis of concurrent iron and vitamin C deficiency was made. On this basis we immediately started replacement therapy with both oral and i.v. ascorbic acid at a daily dose of 3g. This treatment was supplemented with other vitamins, oral iron preparations and a proper diet.

After the first week an evident clinical and hematological improvement was seen, and after four weeks the patient was completely cured and discharged (see Table 1).

This observation, on the one hand, confirms the role played by vitamin C in iron metabo-

Table 1. Hemoglobin levels, iron metabolism parameters and hemoactive vitamin concentrations at presentation and after four weeks of daily intravenous administration of ascorbic acid (3 g/d).

at presentation	*after 4 weeks of ascorbic acid*
Hb = 6.6 g/dL	Hb = 12.6 g/dL
MCV = 87 fL	MCV = 90 fL
serum iron = 26 mg/dL	serum iron = 80 mg/dL
TIBC = 340 mg/dL	TIBC = 356 mg/dL
UIBC = 250 mg/dL	UIBC = 260 mg/dL
serum ferritin = 72 ng/dL	serum ferritin = 80 ng/dL
absolute reticulocytes count = normal	absolute reticulocytes count = normal
vit. B12 = 560 ng/L	vit. B12 = 590 mg/L
folate = 15 mg/L	folate = 16 mg/L
ascorbic acid = 0.22 mg/dL	ascorbic acid = 1 mg/dL

lism, especially with regard to the regulation of iron transport and storage;[5,6] on the other hand, it provides evidence that a hidden, scurvy-like ascorbic acid deficiency has to be kept in mind when considering the possible causes of refractoriness to iron replacement treatment for iron-deficiency anemia.

References

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