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Erythrocyte Folate Does Not Accurately Reflect Folate Status in Sickle Cell Disease

To the Editor:

Optimal folate status of sickle cell disease (SCD) patients might be important because these patients have an inherent high risk of endothelial damage. Serum folate, erythrocyte folate, and plasma homocysteine are used as static and functional markers of folate status.

We recently investigated the folate status of SCD patients (1) and subsequently established the dosages needed for optimal daily supplementation (Van der Dijs et al., submitted for publication). The daily intakes were progressively increased during 70 weeks. During dose escalation, we observed different responses for red blood cell (RBC) folate, but not serum folate, in hemoglobin SS (HbSS) and HbSC patients. These subgroups did not differ in RBC folate at baseline, but the folate concentrations of HbSS patients increased to reach a higher steady state after supplementation. Steady-state concentrations of RBC folate, especially of HbSS patients (n = 10; 1666 ± 273 nmol/L) and to a lesser extent of HbSC patients (n = 7; 1034 ± 504 nmol/L), were higher than those of healthy HbAA adults (n = 67; 771 ± 262 nmol/L) receiving 5 mg of folate for...
4 weeks. The steady-state RBC folate concentrations were significantly different between HbSS and HbSC patients (P = 0.016), and between HbSS patients and HBAA controls (P < 0.0001), as determined by the Student t-test. Our observation is consistent with the establishment of RBC folate concentrations during hemopoiesis and a subsequent decrease during circulation, causing higher RBC folate concentrations in young circulating RBCs (2, 3).

At steady state, subjects with HbSS, HbSC, and HBAA have apparent RBC half-lives of 5–10, 12–25, and 25–40 days, respectively (4). The association with RBC turnover became apparent by an inverse relationship between steady-state RBC folate and Hb (Fig. 1, top) and a positive relationship between steady-state RBC folate and the sum of the RBC polyamines spermidine and spermine (Fig. 1, bottom). The latter is a sensitive marker of mean RBC age, with young RBCs having the highest concentrations (4).

One may argue that the use of special cutoff values, e.g., those derived from HbSS and HbSC patients with optimal folate status, can circumvent the confounding dependence of RBC folate on RBC age. Special cutoff values may, however, cause low sensitivity because of the heterogeneity of RBC turnover in patients classified according to Hb types and the occasional occurrence of hemolytic and vaso-occlusive crises in SCD. For example, patients with concomitant hereditary persistence of HbF will have lower RBC turnover. In addition, the frequently occurring concomitant α-thalassemia also modifies disease activity. It might, therefore, be better to use serum folate and preferably homocysteine for the establishment of folate status, although the latter also depends on vitamins B₁₂ and B₉ and other factors. Our proposal is in accordance with a previous recommendation to use fructosamine and not glycated hemoglobin or HbX₁c in SCD patients because, in contrast to HbX₁c and glycated hemoglobin, fructosamine is not confounded by dependence on RBC turnover rate (4).

References


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Increases of Creatine Kinase MB and Cardiac Troponin T in Serum of a Patient with Uterine Leiomyosarcoma

To the Editor:

A 64-year-old woman with peripheral vascular disease and coronary artery disease presented to a university hospital with a 2-week-old hip fracture, which was operated on the day after the admission. She had had a myocardial infarction 2 years earlier, and the systolic function was slightly reduced. After the operation, the patient had intermittent chest pain. Nitroglycerin had no effect on the pain. The electrocardiogram was unchanged. Cardiac enzymes were followed (Table 1). Unstable angina pectoris was initially suspected, and the patient was treated accordingly.

Because of abdominal pain and vaginal bleeding, she underwent a fractional abrasion, which revealed a uterine tumor and intrauterine pus. She had fever and increased C-reactive protein (352 mg/L) and was treated with antibiotics. A uterine cancer and an abdominal abscess were suspected, and the gynecologist wanted to operate as soon as possible.

Cardiac enzymes were increased (Table 1). There was no biochemical evidence of hepatic or renal failure, and no clinical or x-ray signs of congestive heart failure. The chest pain episodes were atypical of angina pectoris, and serum troponin T (TnT) and creatine kinase MB (CK-MB) were stable during the observation period (Table 1). Cardiac troponin T (cTnT) was analyzed with the third-generation TnT test (Troponin T STAT) on an Elecsys 2010 immunoassay analyzer. The third-generation TnT test uses the same monoclonal antibodies (M11.7 and M7) as the second-generation test but is standardized with human recombinant cTnT instead of bovine cTnT (Roche Diagnostics). CK-MB was measured with an assay that uses two monoclonal antibodies (CKMB STAT) on an Elecsys 2010 analyzer (Roche Diagnostics) by electrochemiluminescence immunoassay.

Would a leiomyosarcoma increase cardiac enzymes in serum? A Medline search of leiomyosarcoma and troponin revealed no such reports. Recently, a metastatic alveolar rhabdomyosarcoma was reported to increase CK-MB and TnT in serum (1, 2). Increased CK-MB was reported in a patient with rhabdomyosarcoma (3), although that patient had received cytotoxic chemotherapy, which might have increased CK-MB in serum. Importantly, our patient received no chemotherapy. CK-MB and CK-BB have been reported in the homogenate of a lung tumor (4).

In our patient, the need for surgery was urgent, and considering the atypical chest pain, the unchanged electrocardiogram, and the sustained enzyme increases, it was felt likely that the increases in the cardiac enzymes were secondary to tumor expression of CK-MB and TnT, despite the lack of such reports previously. A hysterectomy was performed, and a