LOCAL IRON OVERLOAD IN CHRONIC LEG ULCERS

To the Editor

The exact etiology of chronic venous leg ulcers is unknown, however many believe that it is multifactorial. In the May issue of *IMAJ,* Levin and Koren [1] described a patient with thalassemia intermedia who had a chronic leg ulcer that was resistant to treatment and persisted for 14 years. The authors of this case report mention a few of the possible underlying mechanisms that contribute to the pathogenesis of chronic leg ulcer. These include tissue hypoxia secondary to the anemia and to the high affinity of fetal hemoglobin to oxygen, increased rigidity of the diseased erythrocytes, local edema due to venous stasis, repetitive local trauma, and skin infections. Levin and Koren also discussed the role of hypercoagulability and prothrombotic tendency found in thalassemia intermedia patients in the perpetuation of tissue injury around the leg ulcer.

In the picture provided in this report, it appears that the edges of the leg ulcer have a black-brownish pigmentation that is not present in other parts of the surrounding skin of the distal part of the leg. Therefore, I would like to suggest an additional possible pathogenic factor that could have contributed to the chronicity and resistance to therapy of this leg ulcer: local iron overload around the leg ulcer. Increased localized iron overload in chronic venous leg ulcers has been demonstrated by both direct invasive and indirect methods [2,3]. Using diagnostic X-ray spectrometry, a method based on X-ray fluorescence analysis, we demonstrated elevated iron concentration in the skin around the venous ulcers in non-thalassemic patients [2]. Similar findings were demonstrated using direct determination of iron and hemosiderin in skin biopsies from lipodermatosclerotic lesions around the leg ulcers [3]. It has been suggested that extravasations of red blood cells occur as a result of increased venous pressure. Disruption of the erythrocytes and decomposition of the hemoglobin is followed by dermal and subdermal iron deposition, which is stored as hemosiderin.

Data collected in recent years suggest that this form of iron deposition may not be an incidental byproduct, but may actively perpetuate tissue damage in tissues where venous ulcerations occur. The ferric ions (Fe+++) may contribute to the generation of free radicals, activation of metalloproteinase and down-regulation of tissue inhibitors of metalloproteinase. Addionally, it has been suggested that patients who suffer from chronic leg ulcers may have a genetically determined inability to counteract the locally induced iron overload. Correlation was found between the chronicity and size of the leg ulcer and mutations of genes involved in iron metabolism [4].

The patient in this case report was receiving iron chelating therapy for a prolonged period. This form of chelating therapy was probably not enough to reduce the increased iron stores that were present around the leg ulcer. Further research is needed to validate the role of localized iron overload around leg ulcers in patients with thalassemia who suffer already from a generalized form of iron overload.

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SOLUBLE TRANSFERRIN RECEPTORS (STFR) FOR IRON DEFICIENCY DETECTION IN THE ACUTELY ILL, HOSPITALIZED PATIENTS

To the Editor

We read with great interest the article by Berlin et al. on the use of soluble transferrin receptors (sTfR) in the detection of iron deficiency anemia (IDA) in hospitalized patients [1]. In this retrospective study, the authors collected endoscopic data of anemic (but normoferritinemic) inpatients who underwent bidirectional endoscopies because of sTfR levels > 5 mg/L. Although not specifically mentioned in the article, we suspect that in all the patients the mean corpuscular volume (MSV) was normal. The authors found that the majority of patients (22/32, 68%) had significant endoscopic findings to account for the IDA. For 7/32 patients (21.8%), a sinister/malignant cause was found in the upper or lower gastrointestinal (GI) tract. Although the authors mention in Table 1 that 8 patients refused endoscopic investigations, a total of 26 patients with findings are presented.

We had previously reported that, by means of an sTfR-based approach, patients with chronic and/or systemic inflammatory conditions as well as hospitalized patients with a normal ferritin level, i.e., > 50 ng/dl, are frequently iron deficient [2]. In that study, we used the sTfR/$\log_{10}$ ferritin or sTfR-F index to discriminate between IDA and anemia of chronic disease for patients with normal MCV. The index, as Berlin and co-authors point out in their discussion, has been established as a reliable means – superior to other serology markers – for assessing the iron status in a non-invasive way. Furthermore, in a recent systematic review of nine relevant prospective studies (i.e., anemic patients with sTfR measurement coupled with bone marrow aspiration for iron stain), we concluded that sTfR level > 2.5 mg/L is a reliable threshold (with good sensitivity/specificity) for confirmation of IDA [3]. Therefore, I assume that Berlin and

team decided to use an sTfR of 5 mg/L according to the sTfR manufacturer's instructions.

It would also be interesting to know what the mean ferritin level in their cohort was, as well as the endoscopic diagnosis in those two patients with sTfR-F index < 2.0 (we guess > 1.0) [4]. Moreover, was the sinister GI pathology (stomach and colon carcinomas) associated with higher sTfR levels and did the sTfR-F index perform better in this subgroup? In those patients who underwent sTfR measurement and whose levels were < 5.0 mg/L (i.e., within reference range to prompt referral for endoscopies) but still above 2.5 mg/L, was the index reassuring as well? Finally, were the patients in the same subgroup free of GI symptoms? We noted that of the 32 patients, 5 were in hospital for GI investigations (loss of weight, abdominal pain, GI bleeding); therefore, they would have been investigated with endoscopies as part of their regular diagnostic workup, more so if they were also anemic.

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