Iron and calciphylaxis

Sir,

The recent intriguing paper by Farah et al. [1] observed that in tissue blocks taken from 12 patients with chronic kidney disease diagnosed with calciphylaxis, iron deposition was present in areas of microvascular calcification in all cases and was absent in unaffected microvasculature. The authors appropriately caution that the observed association between iron and calcium deposition does not prove causality and they do not propose that iron deposition is the sole factor inducing calciphylaxis. However, they raise the hypothesis that iron therapy may increase vascular oxidative stress and predispose to calciphylaxis in the uremic setting and that metal chelation may have a role in treatment. Isolated patient case reports have linked iron deposition to tissue calcification [2, 3].

Calciphylaxis is a rare clinical event. We analyzed data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [4] to consider a possible connection between iron therapy and calciphylaxis. The DOPPS is a very large, prospective observational study of hemodialysis patients in 12 nations. We hypothesized that if iron predisposes to calciphylaxis, then patients diagnosed with calciphylaxis may have been exposed to greater iron burdens than others. Kalantar-Zadeh et al. [5] have reported that intravenous iron doses >400 mg/month are associated with higher risk of mortality among hemodialysis patients, so we examined <400 versus ≥400 mg/month. Among 19 596 patients followed between 2002 and 2008, 2053 (11%) had received ≥400 mg/month over a 4-month baseline period. However, among the 56 individuals who were hospitalized with a new diagnosis of calciphylaxis, 9 (17%) had received ≥400 mg/month during the 4-month period preceding hospitalization. Thus, it is possible that high-dose iron treatment increases the likelihood of calciphylaxis (odds ratio = 1.59, P = 0.20). Among patients with calciphylaxis-related hospitalization, 41% had serum ferritin concentrations ≥500 ng/mL compared with 35% of patients at baseline in the full study sample (P = 0.40). The mean ferritin concentration prior to calciphylaxis was 492 ± 5 (SE) versus 460 ± 3 ng/mL at baseline for the overall group (P = 0.17). If iron truly predisposes to calciphylaxis, the very small number of calciphylaxis events make it difficult to establish the association with statistical significance even in a large research database such as the DOPPS.

These findings, though clearly not definitive, are consistent with the possibility of an iron-induced predisposition to calciphylaxis, as hypothesized by Farah et al., and merit additional investigation.

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