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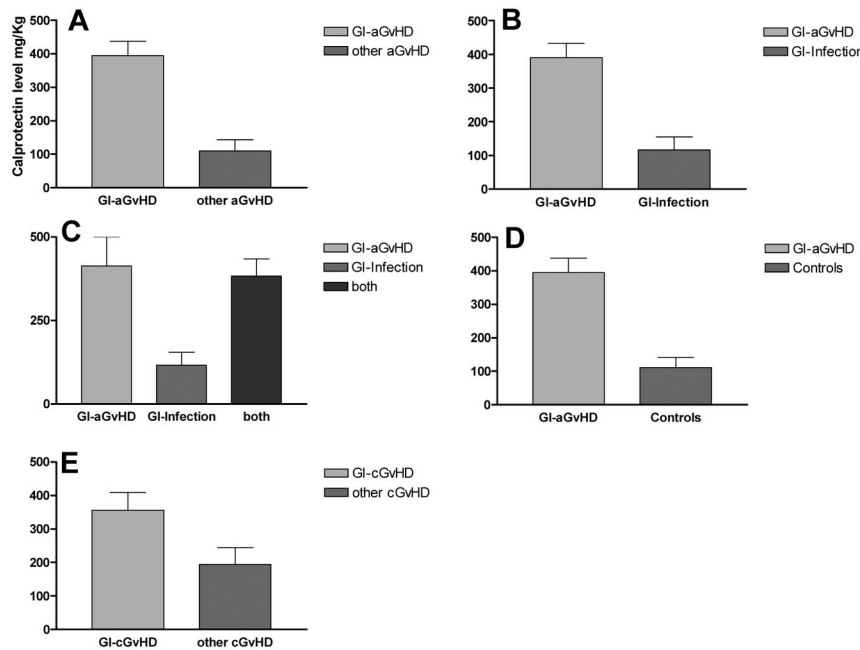
## To the editor:

### Role of fecal calprotectin as biomarker of gastrointestinal GVHD after allogeneic stem cell transplantation

We read with interest the article of Rodriguez-Otero et al.<sup>1</sup> The authors studied the ability of fecal calprotectin (FC),  $\alpha$ -1 antitrypsin, and elastase to diagnose acute gastrointestinal GVHD (GI-GVHD) after allogeneic stem cell transplantation (SCT). In their experience, FC and  $\alpha$ -1 antitrypsin increased in patients with GI-GVHD, but there was no statistic difference compared with control groups. On the other hand, high levels of both markers at the time of diagnosis were predictive of steroid-resistant GVHD. In past years, our group also investigated the role of FC as a noninvasive biomarker of GVHD. We enrolled a cohort of 59 hematologic patients consecutively submitted to allogeneic SCT, and studied the level of FC in patients who developed GI-GVHD, non-GI-GVHD, and in patients with infective colitis. We also included a control group of 9 patients with aspecific colitis after autologous SCT. FC was detected at the onset of symptoms and before starting any therapy. Stool collection was performed by Calprest device and the protein level was measured by ELISA

assay (Calprest test; Eurospital). Data were analyzed using IBM SPSS Statistics 20 Core System and Prism Version 3.0 software (GraphPad). Diagnosis and staging of acute GVHD (aGVHD) and chronic GVHD (cGVHD) was made according to current criteria.<sup>2,3</sup> FC was higher in patients with acute GI-GVHD (GI-aGVHD) than in non-GI-aGVHD (500 mg/Kg vs 95 mg/Kg;  $P = .0003$ ; Figure 1A), and in stage III-IV GI-aGVHD than in the others; although, no statistic difference was observed in this case.

After treatment, in 2 of 3 responsive patients, FC value decreased to less than 15 mg/Kg. In contrast, FC was lower in patients with infective colitis compared with GI-aGVHD (106 mg/Kg vs 500 mg/Kg;  $P = .0039$ ; Figure 1B). Comparing patients with GI-aGVHD, patients with infective enteritis and patients with both conditions, the median level of FC was 500 mg/Kg, 106 mg/Kg, and 475 mg/Kg, respectively ( $P = .0096$ ; Figure 1C). FC was also lower in the control group of patients submitted to autologous SCT who developed mucositis and



**Figure 1. FC levels in different settings.** (A) FC in patients with GI-aGvHD and other organ involvement aGvHD. (B) FC in patients with GI-aGvHD and infective enteritis. (C) FC in patients with GI-aGvHD, infective enteritis and concomitant GI-aGvHD, and infective enteritis. (D) FC in patients with GI-aGvHD and patients with diarrhea after autologous SCT. (E) FC in patients with GI-cGvHD and other organ involvement cGvHD.

diarrhea with a FC median level of 92 mg/Kg versus 500 mg/Kg ( $P = .0012$ ; Figure 1D). Furthermore, we analyzed FC level at the onset of cGVHD. Again it was higher in patients with GI involvement than in non-GI-cGVHD (450 mg/Kg vs 94.5 mg/Kg;  $P = .0229$ ; Figure 1E). Although no statistic difference was seen, FC was higher for score-3 GI-cGVHD than in score-2 (475 mg/Kg vs 171.5 mg/Kg, respectively). Using an arbitrary cut-off point value of 160 mg/Kg, sensitivity of the test was 100%, specificity 81.8% with a positive predictive value of 86%, and a negative predictive value of 100%. The area under receiver operating characteristic (ROC) curve for the test was 0.942 (confidence interval: 0.848-1.000). Consistent data are recently reported also by Bastos Oreiro et al.<sup>4</sup> In conclusion, fecal calprotectin could be considered as a possible sensitive marker of GI-GVHD given its ability to distinguish GI-GVHD manifestation from other causes of diarrhea, such as infective colitis or aspecific enteritis. Moreover, fecal calprotectin was a noninvasive test and samples could be easily collected by patients themselves or by the nursing staff.

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