

SERUM LEVELS OF β 2 MICROGLOBULIN AND INTERLEUKIN-6 TO DIFFERENTIATE MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

To the Editor:

We would like to comment on the recent letter from Greco et al.¹ They mistakenly claim that we²⁻⁴ presented serum levels of β 2 microglobulin (β 2M) and of interleukin-6 (IL-6) as clinically useful parameters to discriminate individuals with monoclonal gammopathy of undetermined significance (MGUS) from those with early multiple myeloma (MM). About β 2M, we clearly stated that (1) "it was impossible to separate normal individuals, patients with benign monoclonal gammopathy and patients with low mass MM" (ie, using β 2M)²; (2) "serum β 2M cannot clearly distinguish MGUS from early MM in an individual patient"³; and (3) "serum β 2M cannot be used as a discriminant test to differentiate the two conditions" (ie, MGUS from early MM).⁵ We made no specific comments about IL-6,⁴ but clearly noted that both β 2M and IL-6 were related to disease severity and had strong prognostic value in patients with overt MM.^{4,5} These data are confirmed by the large studies from the Medical Research Council (UK) and the Southwest Oncology Group (United States) for β 2M, and by Ludwig et al⁶ and Reibnegger et al⁷ for IL-6. Finally, the prognostic value of IL-6 was recently confirmed by discovery of the strong prognostic value of C-reactive protein (CRP), an IL-6–dependent acute phase protein, in patients with overt MM.^{8,9} Like β 2M and IL-6, CRP does not discriminate between benign monoclonal gammopathy

and early MM.⁹ It is clear for all experts that the problem of differentiating MGUS from early MM is difficult. Measurement of the plasma cell labeling index¹⁰ and evaluation of plasma cell-induced bone changes¹¹ or of plasma cell phenotype (CD56 expression)¹² may help, but no single technique really differentiates benign from malignant plasma cell proliferation (see Kyle¹³ for a recent review).

Another point in the letter of Greco et al¹ is that 81.5% of their patients with MGUS had neoplastic disease. It is now well documented that several epithelial tumors can produce or use IL-6 as a tumor growth factor.¹⁴ The best example is renal cell carcinoma for which IL-6 is an autocrine growth factor, CRP a strong prognostic factor, and anti-IL-6 therapy a currently investigated treatment.¹⁵⁻¹⁷ More importantly, the associated MGUS status can be greatly improved by nephrectomy.¹⁸ Thus, their MGUS population is not the usual one that could account for its increased IL-6 and CRP serum levels, similar to the increased β 2M serum levels which commonly occur in patients with cancer.

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