Prognostic Impact of Serum Heavy/Light Chain Pairs in Patients With Monoclonal Gammopathy of Undetermined Significance and Smoldering Myeloma: Long-Term Results From a Single Institution

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Abstract

The aim of the present study was to investigate the prognostic effect of involved and uninvolved heavy/light chain (HLC) pair and HLC ratios on progression in 114 patients diagnosed with smoldering myeloma and monoclonal gammopathy of undetermined significance from 1983 to 2003. The evolving pattern and suppression of any IgM HLC pair were associated with a shorter time to progression. The novel HLC assay is a valuable tool in the risk stratification of these patients.

Background: Asymptomatic monoclonal gammopathies, such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM), are clinical conditions that usually precede symptomatic multiple myeloma. Therefore, risk stratification is crucial owing to the heterogeneous progression rate among these patients. In previous years, suppression of the uninvolved chain of specific heavy/light chain (HLC) pairs in serum has been identified as a new risk factor in MGUS. The aim of the present study was to investigate the prognostic effect of involved and uninvolved HLC pairs and HLC ratios on progression in a series of patients with MGUS and SMM. **Patients and Methods:** All specific serum HLC pairs were measured in 114 patients diagnosed with SMM (n = 27) and MGUS (n = 87) from 1983 to 2003. Also, the HLC ratios were calculated. **Results:** Progression to symptomatic multiple myeloma was observed in 13 patients (8 with SMM and 5 with MGUS). The risk of progression was 6 times greater in those with SMM ($P = .001$) and 4 times greater for those with the IgA isotype ($P = .01$). The suppression of any IgM isotypes (IgMκ or IgMλ) in patients with IgA or IgG gammopathy or any IgA isotypes (IgAκ or IgAλ) in patients with IgG or IgM gammopathy was associated with a shorter time to progression to symptomatic gammopathy ($P = .001$ and $P = .03$, respectively). On multivariate analysis, the evolving pattern and suppression of any IgM HLC pair remained significant. **Conclusion:** HLC ratios could be a valuable tool in the risk stratification of patients with SMM and MGUS, especially patients with IgG isotypes.

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Introduction

Asymptomatic monoclonal gammopathies, such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM), are clinical conditions that usually precede symptomatic multiple myeloma (MM).[1-3] Therefore, risk stratification is crucial owing to the heterogeneous progression rate

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among patients with these entities.[4] This is particularly important when chemoprevention trials are encouraged for high-risk patients.[5] Thus, biomarkers and the prognostic index based on the tumor load (serum M-spike amount, detection of urinary monoclonal light chain, and percentage of bone marrow plasma cells),[6] M-protein behavior (evolving vs. nonevolving),[7,8] and/or immunologic status (heavy chain isotype, suppression of uninvolved immunoglobulins, and serum free light chain [FLC] κ/λ ratio),[9-11] among others, have been identified.[12-15]

In addition to the identification of total serum immunoglobulins, novel antibodies for quantification of specific pairs of heavy/light chains (HLC pair; IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, and IgMλ) in serum have been developed.[15-17] Their use can improve the accurate identification of the involved (monoclonal) and uninvolved (polyclonal) immunoglobulins, allowing the calculation of a ratio (HLC ratio) between the monoclonal and polyclonal immunoglobulins (ie, the IgGκ/IgGλ ratio in patients with IgGκ gammopathy) similar to the calculation of the serum FLC ratio.[18] This permits a more precise quantification of tumor immunoglobulin. Uninvolved HLC pair suppression was described as an independent predictor of progression to MM in patients with MGUS, which can occur years before overt malignant transformation.[9]

The aim of the present study was to investigate the prognostic effect of involved and uninvolved HLC pairs and HLC ratios on progression in a series of patients with MGUS and SMM with long follow-up data available.

Patients and Methods

A total of 114 patients (median age, 61 years; 44 men, 70 women) diagnosed with SMM (n = 27) or MGUS (n = 87) at a single institution from 1983 to 2003 were included in the present study. The criterion to include patients in the present study was that they had ≥ 1 frozen serum sample taken during the follow-up period.

The median follow-up period for the living patients was 13.7 years (range, 7-27 years). Of the 27 patients with SMM, 11 met both of the original diagnostic criteria (bone marrow plasma cell infiltration of ≥ 10% and serum M-protein of ≥ 30 g/L). We stratified MGUS (serum M-protein, non-IgG isotypes) and SMM (bone marrow plasma cells, serum M-protein) risk using the original criteria from the Mayo Clinic.[6] However, the serum FLC ratio was not available for historical reasons because our institution did not begin to use it systematically until 2009. Progression in patients with MGUS/SMM to symptomatic MM was assessed according to the International Myeloma Working Group criteria.[12] In accordance with standard clinical practice and local protocols, patients with MGUS were routinely evaluated once annually when they had stable disease, and patients with SMM were evaluated every 3 months.

HLC pairs were quantified in grams per liter using immunonephelometry in a Dade Behring BN II Nephelometer (Siemens). Polyclonal sheep antibodies (provided by The Binding Site, Birmingham, UK) were used as previously described.[16] Serum samples were stored frozen at −80° C and were only thawed for the present study.

We used the following definitions in the present study. The HLC pair was defined as the specific pair of heavy/light chain (IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, IgMλ) evaluated by immunonephelometry (Hevylite; The Binding Site, Ltd.). Uninvolved HLC pair suppression was defined as the values of the uninvolved HLC pair were lower than the normal values reported by Bradwell et al.[16] Therefore, in a patient with IgGκ gammopathy, we considered uninvolved HLC pair suppression to be present when the values of the IgGλ, IgAκ, IgAλ, IgMκ, or IgMλ pair were lower than the normal values.[16] The HLC ratio was defined as the ratio between the monoclonal and polyclonal immunoglobulins of the same isotype (ie, IgGκ/IgGλ in patients with IgGκ gammopathy).[16] An abnormal HLC ratio was considered present when the HLC ratios were lower or higher than the normal HLC ratios.[16,17] A reduction of the total serum immunoglobulin was defined as those values less than normal in our laboratory using nephelometry (normal IgG, 6.8-15.3 g/L; normal IgA, 0.66-3.65 g/L; and normal IgM, 0.36-2.61 g/L). Immunoparesis for total immunoglobulins was considered present if the patient had a reduction of the uninvolved total serum immunoglobulin (ie, reduced IgA and/or IgM total serum immunoglobulin in a patient with IgG gammopathy). An evolving pattern of SMM was defined by an increase in the M-protein level of ≥ 10% in the first 6 months of follow-up after the diagnosis.[8] Finally, an evolving pattern of MGUS was defined as a progressive increase of ≥ 10% in the M-protein level at the annual follow-up visit during the first 3 years.[7]

Statistical tests were performed with SPSS software, version 20.0, for Windows. Categorical variables were contrasted by χ^2 or Fisher exact test and median differences using analysis of variance or the *t* test. Survival probabilities were estimated using the Kaplan-Meir method and compared using the log-rank test. The Cox proportional hazards model was used to estimate the risk ratio of events (relative risk) with the respective confidence interval (CI) and multivariate analysis. The ethics committee of the Hospital Clínic of Barcelona approved the present study.

Results

Clinical Outcomes

The clinical characteristics of the present series are summarized in Table 1. The mean age of the whole group at diagnosis was 61 years (range, 37-82 years). Only 2 patients (1.7%; 1 with MGUS and 1 with SMM) had only light-chain M-protein. The median bone marrow plasma cell infiltration was 4% and 15% in the MGUS and SMM groups, respectively. The risk stratification according to the Mayo Clinic criteria and evolution of patients with SMM/MGUS in our series are detailed in Table 2. Of the patients with MGUS, 42 (48%) did not have any risk factor and only 10 patients (12%) had 2 risk factors. In contrast, ≤ 41% of patients with SMM had 2 risk factors (bone marrow infiltration plus serum M-spike).

Progression to malignant symptomatic gammopathy was observed in 13 patients (11%; 8 with SMM and 5 with MGUS), mainly to MM,[11] with exception of AL amyloidosis and Waldenström's macroglobulinemia in 1 case each. Of the patients with progression to MM, 6 had IgGκ, 4 had IgAκ, and 1 patient had IgAλ. The patient with progression to AL had IgGλ and the patient who developed Waldenström's macroglobulinemia was IgMκ. The risk of progression was 6 times greater for patients with SMM than for those with MGUS (hazard ratio [HR], 6.2; 95% CI, 2.1-19.7; $P = .001$). No progression was observed in patients with SMM and