Monoclonal gammopathy of undetermined significance: new insights

Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med* 2002;346:564-9.

Background: A monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of serum monoclonal protein without evidence of multiple myeloma or related disorders. MGUS is relatively common among older people, occurring in up to 2% of those over 50 years of age and in about 3% of those over 70. Previous studies indicated that about 25% of cases will progress to multiple myeloma or a related cancer after a mean of 10 years.[1] However, these were smaller studies, and there is currently no reliable predictor of progression.

Question: When MGUS is diagnosed, what is the risk of progression to multiple myeloma or related cancers, and what factors are predictive of progression?

Methods: This observational study identified patients from the 11 counties in southeastern Minnesota in whom MGUS was diagnosed at the Mayo Clinic from 1960 to 1994. MGUS was defined by the following criteria: a serum monoclonal protein level of 30 g/L or less; no monoclonal protein or only moderate amounts of monoclonal light chains in the urine; the absence of lytic bone lesions, anemia, hypercalcemia and renal insufficiency related to the monoclonal protein; and a proportion of plasma cells in the bone marrow of less than 10%. A bone marrow examination was optional, unless the monoclonal protein level was greater than 20 g/L or the patient had unexplained symptoms or signs.

The medical records of the patients were reviewed, as were all death certificates. The primary end point was progression to multiple myeloma or another type of B-cell or lymphoid cancer.

Results: In the study, 1395 patients with MGUS were identified, and all but 11 gave permission to have their medical records reviewed. The 1384 study patients had a mean age of 72 years at diagnosis, and the monoclonal protein was identified as IgG in 70% of cases. During the 11 009 person-years of follow-up (median 15.4 years, range 0–35 years) the MGUS progressed in 115 patients (8%) to multiple myeloma, lymphoma with an IgM serum monoclonal protein, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia or plasmacytoma. The cumulative probability of progression to any plasma-cell cancer was 12% at 10 years, 25% at 20 years and 30% at 25 years. The cumulative probabilities of progression to multiple myeloma at 10, 20 and 25 years were 10%, 21% and 26% respectively. The relative risk of multiple myeloma, on the basis of expected incidence rates in the general population, was 25.0 (95% confidence interval 20–32).

Among many baseline factors evaluated with respect to predicting the progression to myeloma or related cancers, only the concentration and type of monoclonal protein were independent predictors. For example, the risk of progression to myeloma or related cancers at 10 years was 6% for an initial monoclonal protein concentration of 5 g/L, 7% for 10 g/L, 11% for 15 g/L, 20% for 20 g/L, 24% for 25 g/L and 34% for 30 g/L. Patients with IgM or IgA monoclonal protein had a higher risk of progression to disease than those with IgG monoclonal protein.

Commentary: This was not a population-based study, because the 1395 patients with MGUS were identified through the medical records of a tertiary care centre. Therefore, the results may be subject to referral bias — there is a tendency to refer patients with more severe disease, leading to an overestimation of the risk of progression to disease within the community.

Implications for practice: The cumulative probability of progression from MGUS to multiple myeloma or related cancers is about 1% per year. The risk of progression does not disappear after the condition has remained stable for a few years after diagnosis, as was once believed; therefore, follow-up should continue over the long term. Annual serum protein electrophoresis and hemoglobin, creatinine and calcium measurement is a reasonable approach, but patients with higher concentrations of monoclonal protein or new symptoms should be monitored more closely. Elderly patients with MGUS are nevertheless more likely to die of unrelated causes, such as cardiovascular disease, stroke or a non-plasma-cell cancer.

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Reference

1. Kyle RA. "Benign" monoclonal gammopathy — after 20 to 35 years of follow-up. *Mayo Clin Proc* 1993;68:26-36.