CASE STUDY

Monoclonal Gammopathy of Undetermined Significance
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Abstract: Monoclonal gammopathy of undetermined significance is not a benign condition. There is a significant increase in mortality associated with the risk of development of multiple myeloma and related disorders.

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Case Presentation
A fifty-three year old female applied for one million dollars of whole life insurance. On the application she admitted a history of “monoclonal gammopathy of undetermined significance” for several years. She had quit smoking cigarettes over 20 years prior. A medical examination by a physician revealed a height of 5'5", weight 130 pounds, blood pressure 108/66. There were no significant findings on the physical examination, including a negative dipstick for urine protein and glucose. A blood profile was limited due to inadequate quantity so that total serum protein and globulin were not reported but was otherwise normal (including an alkaline phosphatase of 76 U/L (normal range 20-115), BUN 20 mg/dl (5-25) and serum creatinine 0.7 mg/dl (0.5-1.7). The urine specimen was negative for protein. Attending physician reports were obtained.

The applicant had been followed for her diagnosis of monoclonal gammopathy of undetermined significance (MGUS) for about eight years. No details were available as to the reason it was first detected other than there were “abnormal blood tests” found in association with an allergy evaluation. As early as six years prior she had been evaluated extensively.

More recent followup in the prior year included a negative ANA, negative rheumatoid factor, and beta-2-microglobulin 1.6 (normal < 2.4 mg/dl). Serum protein electrophoresis was reported as a monoclonal spike in the gamma region with total protein 6.90 gm/dl (6.0-8.3), albumin 3.85 g/dl (3.0-5.0), alpha 1 globulin 0.28 gm/dl (0.12-0.50), alpha 2 globulin 0.74 gm/dl (0.5-1.1), beta globulin 0.73 gm/dl (0.6-1.3), and gamma globulin 1.3 gm/dl (0.5-1.6). Immunoelectrophoresis of the urine showed the presence of monoclonal IGG lambda with monoclonal lambda free light chains (Bence-Jones Protein). A bone marrow aspirate revealed a myeloid to erythroid ratio of 4:1; blast count < 5%, lymphocytes and plasma
cells accounting for 10-12% of marrow cellularity, no obvious lymphoplasmacytosis; overall, a bone marrow not consistent with multiple myeloma. A CT scan of the vertebra was negative for lytic lesions. Other pertinent laboratory results include alkaline phosphatase 73 IU/L, SGOT/AST 17 IU/L (10-42), SGPT/ALT 17 IU/L (10-60), BUN 12 mg/dl (6-20), calcium 10.0 mg/dl (8.5-10.0), hemoglobin 13.0 gm/dl, hematocrit 38.6%, platelets 350 K/UL, white blood cells 4.3 K/UL with differential: lymphocytes 45.8% (21.8-41.6), monocytes 8.8% (5.7-14.0), granulocytes 42.7% (49.2-70.4), eosinophils 2.1% (0.0-8.0), and basophils 0.6% (0.0-1.5).

Discussion
Monoclonal gammopathy of undetermined significance (MGUS) is one of a group of plasma cell disorders that includes both neoplastic and potentially neoplastic disorders. All are associated with the proliferation of a single clone of immunoglobulin-secreting plasma cells derived from B lymphocytes. Monoclonal gammopathy, monoclonal gammopathy of undetermined significance (MGUS), benign monoclonal gammopathy, immunoglobulinopathy, paraproteinemia and dysproteinemia are sometimes used interchangeably to describe the presence of a M-protein (monoclonal protein) without evidence of multiple myeloma, macroglobulinemia, amyloidosis or other related diseases. The most accepted term is monoclonal gammopathy of undetermined significance.

MGUS is characterized by a serum M-protein concentration less than 3 grams per deciliter; fewer than 5% to 10% plasma cells in the bone marrow (there is variation of opinion in the literature from as low as 5% to as high as 20%); only a small amount of M-protein in the urine; absence of lytic bone lesions, anemia, hypercalcemia and renal insufficiency; and stability over time of the M-protein.

Differentiation of MGUS from multiple myeloma, macroglobulinemia or a related disorder is difficult when the M-protein is first discovered. The M-protein concentration is often most helpful: levels greater than 3 grams per deciliter usually indicate overt multiple myeloma or macroglobulinemia. Levels of immunoglobulin not associated with the M-protein are almost always reduced in multiple myeloma or Waldenstrom's macroglobulinemia.

Monoclonal proteins are found in 1% of patients over 50 years old and in 3% over 70 years old. They are often described as benign when their evaluation fails to reveal more serious conditions. The discovery of the monoclonal protein occurs for a variety of reasons. It is seldom made from the discovery of Bence-Jones proteinuria. Bence-Jones proteins are not detected by the urine dipsticks commonly used in examinations although they are detected by many laboratory assays including those used by insurance laboratories if there is sufficient concentration of the Bence-Jones proteins. The detection of most occurrences of Bence-Jones proteins require the use of very sensitive immunoassays.

The most comprehensive published survival data for MGUS has been from Kyle at the Mayo clinic. Their published series includes 241 patients with MGUS that were followed for 20 to 35 years with a median of 22 years. By 5 years 11% had developed multiple myeloma, macroglobulinemia, amyloidosis or other related diseases. The most accepted term is monoclonal gammopathy of undetermined significance.

Survival curves for this population compared favorably to U.S. population curves. Data
was not available to make a direct comparison to life insurance populations. However, several conclusions can be made about the mortality experience of this subpopulation: The more favorable than expected mortality experience in this subpopulation is a function of the age of the entrants. The median age at diagnosis of MGUS in this series was 64 years, so that it is expected at 10, 20 and 30 year intervals that many individuals will have died secondary to unrelated causes. This is the case with this series where half died of unrelated causes. Age does not appear to be a prognostic factor so that the annual risk of conversion of one to two percent or the equivalent of 10/1000 to 20/1000 closely equates the annual risk of increased mortality in this subpopulation. As noted by Singer, fixed extra annual mortality has a diminishing impact on annual mortality as age increases (the added expectation of death (Δq) is fixed but the expected q (annual death rate) rises with age so that the impact of the (Δq) on the total q diminishes with time (Δq/q + Δq)5).

Summary
1. The diagnosis of MGUS is based on the presence of a serum M-protein concentration less than 3 grams per deciliter; fewer than 5% to 10% plasma cells in the bone marrow; only a small amount of M-protein in the urine (or none); absence of lytic bone lesions, anemia, hypercalcemia and renal insufficiency; and stability over time of the M-protein.

2. The diagnosis of MGUS is provisional for the first year. Most authors advise repeating evaluation at six months and one year and then at least each year thereafter. There appears to be a slight rise in the annual rate of conversion to more serious disorders, from 1% annually in the first 5 years to 2% annually at 15 years.

3. There are no prognostic indicators once the diagnosis of MGUS is made to differentiate the degree of risk of conversion.

4. Conversion to a more serious plasma cell disorder is often sudden and fatal. The one year survival of multiple myeloma is 70% and the five year survival is 30%.

5. The increase in the annual mortality rate in one series is in the range of 10/1000 to 20/1000. Although it appears to be age independent, most data is based on individuals over the age of 50. There is insufficient information to suggest whether or not this is applicable to younger individuals.

This individual meets the criteria for the diagnosis of MGUS. Her clinical course has been apparently stable for eight years. Her age is at the lower range of individuals with this disorder but the expected additional mortality is significant. It can be expected to be 10/1000 to 20/1000 annually for the remainder of her life.

References