WALDENSTROM`S MACROGLOBULINAEMIA

Essay

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By

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INTRODUCTION

Paraproteinemias are characterized by the presence of monoclonal immunoglobulins in the serum and/or urine. Monoclonal immunoglobulins are commonly referred to as monoclonal proteins, M proteins, or paraproteins. The presence of M proteins is indicative of a clonal plasma cell proliferative disorder such as myeloma, monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom`s macroglobulinemia (WM), etc; additional tests are required to distinguish between the various plasma cell disorders ***(Kyle et al., 2003).***

The paraprotein is a monoclonal immunoglobulin or light chain present in the blood or urine; it is produced by a clonal population of mature B cells, most commonly plasma cells. Paraproteinaemias represent a group of related diseases chracterized by an unbalanced or disproportionate proliferation of immunoglobulin-producing cells, usually from a single clone. These cells frequently secrete a structurally homogeneous immunoglobulin (M-component) and/or an abnormal immunoglobulin. This paraprotein affects immunity and can lead to hyperviscosity, amyloidosis and renal impairment ***(Cook and Macdonald, 2007).***

Recently published population based studies from Minnesota have clarified the incidence of paraproteinaemia in

the general population on individuals aged >50 years, the overall incidence of a paraprotein is 3.2%; this varies with age (age 50–59, 1.7%; age >70, 5.3%) and sex (men: women, 4.0%: 2.7%). There is also an ethnic variation with previous reports noting the age adjusted prevalence of MGUS being threefold higher in African Americans than the white population. Paraproteins are therefore a common laboratory finding in an elderly population ***(Landgren et al., 2006).***

A wide range of mature B cell disorders may be associated with a circulating paraprotein. In a review of more than 1000 cases of M protein seen at the Mayo Clinic the underlying diagnosis was MGUS (51%), Multiple myeloma (MM) (18%), AL amyloidosis (11%), lymphoproliferative disorder (4%), and other disorders such as smouldering myeloma or solitary plasmacytoma (16%). The lymphoproliferative disorders chronic lymphocytic leukaemia (CLL) and lymphoplasmacytic lymphoma/ WM generally have associated clinical and laboratory features which greatly facilitate diagnosis. CLL can infrequently be associated with a paraprotein ***(Kyle et al., 2006).***

There are many causes of paraproteinemias, we will give an overview about them.

Table (1): Benign and malignant causes of paraproteinemias

Benign causes	Malignant causes
1- MGUS. 2- Cryoglobulinemia. 3- Cold agglutinin disease. 4- PCH. 5- Warm antibody AIHA. 6- Others systemic diseases: rheumatoid arthritis- scleroderma- Hashimoto thyroiditis- pyoderma gangrenosum-necrobiotic xanthogranulomatosis- hepatitis- cirrhosis-tuberculosis- bacterial endocarditis and miscellaneous syndromes eg; Schnitzler syndrome.	1- MM. 2- WM. 3- B-CLL. 4- POEMS syndrome. 5- HCDs. 6- NHL.

(Ong et al., 2007)

WM is a rare chronic B-cell lymphoproliferative disorder characterised by a monoclonal IgM paraprotein and morphological evidence of LPL. It is regarded as a low grade NHL. It is considered one of the causes of malignant paraproteinaemia ***(Bjorkholm, 2004).***

The overproduction of IgM causes hyperviscosity of blood, interfering with circulation through small blood vessels. It is characterized by the prescence of IgM monoclonal gammopathy, bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation, Intertrabecular pattern of bone marrow infiltration, surface IgM+ CD5- CD10- CD19+

CD20+ CD22+ CD23- CD25+ CD27+ FMC7+ CD103- CD138 by immunophenotyping ***(Johnson et al., 2006).***

A significant minority of patients remain asymptomatic and never require therapy while others have advanced lymphoma requiring therapy. Adverse prognosis is associated with advanced age, male sex, the prescence of general symptoms (e.g. weight loss), lymphadenopathy, hepatomegaly, previous therapy, disease duration longer than 1 year, Low haemoglobin level, low white cell count, low platelets, high beta-2 microglobulin; low serum IgM, low albumin, presence of cryoglobulinemia, high ESR ***(Chen, 2004).***

AIM OF THE WORK

To give an overview about paraproteinaemias with highlights on Waldenstrom`s Macroglobulinaemia.

CAUSES OF PARAPROTEINEMIAS

1. Monoclonal gammopathy of undetermined significance:

MGUS is characterized by a serum M protein concentration of less than 30 g/L, fewer than 10% clonal plasma cells in the bone marrow, and the absence of end-organ damage that can be attributed to the plasma cell proliferative disorder. End-organ damage is defined by hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) related to the plasma cell proliferative disease ***(Goodman et al., 2003).***

The prevalence of MGUS was 3.2% in 21,463 predominantly white residents of Olmsted County, Minnesota, who were 50 years of age or older. The prevalence was 4.0% in men and 2.7% in women, 5.3% in persons 70 years of age or older, and almost 9% in men older than 85 years of age. Despite the common occurrence of MGUS, it is markedly underdiagnosed in the general population because this condition is asymptomatic and does not produce the signs or symptoms of multiple myeloma or related disorders. They found that the prevalence of MGUS in Olmsted County was 3.8% in persons 70 years of age, but that the prevalence of clinically detected cases at this age was only 0.8%. Thus, only 21% of patients with MGUS at the age of 70 were detected by clinical practice in Olmsted County. In contrast, at the age of 80, 33% of patients with MGUS were detected by routine clinical practice, while the clinical detection rate was only 8% in those 50 years old. Overall, only 22% of patients with a known

MGUS were recognized by routine clinical practice in Olmsted County, Minnesota ***(Kyle et al., 2007).***

The prevalence of MGUS in African Americans and Africans is approximately double that in whites. The prevalence in Japan is lower than in whites ***(Iwanaga et al., 2007).***

The cause of MGUS is not known. In a report of atomic bomb survivors, those exposed to high levels of radiation at a young age had an increased risk of MGUS. Pesticides have also been implicated. In a study of pesticide applicators living in Iowa or North Carolina, the age-adjusted prevalence of MGUS was 1.9-fold higher than in men from Minnesota ***(Landgren et al., 2009).***

A 3-fold or greater risk was found in users of dieldrin, a chlorinated insecticide and the carbon-tetrachloride-carbon disulfide fumigant mixture. There was also an increased risk of MGUS in those exposed to the fungicide chlorthalonil. There is also a genetic element. A report on 247 first-degree relatives of 97 MGUS patients showed an approximate 2-fold higher risk of MGUS in first-degree relatives ***(Vachon et al., 2009).***

What is the importance of MGUS? Is it simply an interesting laboratory finding or is it of importance to the patient? Prior to 1978, the presence of an asymptomatic M protein was often referred to as benign monoclonal gammopathy. In that year, the findings of a study of 241

patients with a monoclonal gammopathy was published but no evidence of MM, WM, AL amyloidosis or a lymphoproliferative disorder. So, the term MGUS is used to describe such patients because MM or a closely related plasma cell disorder developed at a rate of 1.5% per year, indicating that the condition was not entirely benign. This cohort was followed up for 3,579 person-years of observation. Sixty-four patients (27%) developed multiple myeloma or a related disorder. The interval from the recognition of MGUS to diagnosis of multiple myeloma or a related disorder ranged from 1 to 32 years (median 10.4 years). The risk of progression, which was 1.5% per year, was still continuing without change after 25 years of observation ***(Kyle et al., 2004).***

A study of 1,384 patients with MGUS from the 11 counties of Southeastern Minnesota evaluated at the Mayo Clinic from 1960 to 1994 is conducted. The median age at diagnosis was 72 years, which is 8 years older than that of the original cohort of 241 patients. During a follow-up of 11,009 person-years (median 15.4 years; range, 0 to 35 years), 70% died, indicating a mature follow-up. MM, AL amyloidosis, lymphoma with an IgM serum protein, WM, plasmacytoma or CLL developed in 115 patients (8%). The cumulative probability of progression was 10% at 10 years, 21% at 20 years, and 26% at 25 years. Thus, the risk of progression was approximately 1% per year. These patients were at risk of progression, even after more than 25 years of follow-up. The

number of patients with progression to a plasma cell disorder (n=115) was 7.3 times the number expected. The risk of developing MM was increased 25-fold, that of developing WM 46-fold, and that of AL amyloidosis 8.4-fold. The risk of lymphoma was moderately increased at 2.4-fold, but this risk was underestimated because only lymphomas associated with an IgM protein were counted in the observed number, while the incidence rates for lymphomas associated with IgG, IgA, and IgM proteins were used to calculate the expected number ***(Kyle et al., 2003).***

The finding that MGUS predisposes to MM raises the question of whether MM is always preceded by a MGUS or whether the disease can arise de novo. In clinical practice, data from the Mayo Clinic series of 1,027 consecutive patients with MM suggest that only 20% of these patients had a known prior diagnosis of MGUS. Another study is done by the USA PLCO (prostate, lung, colorectal, and ovarian) Cancer Screening to address this question. In this study of 77,469 people who were cancer-free, they identified 71 individuals who subsequently developed MM during the study in which serially collected serum samples were obtained from 2 years to 9.8 years prior to the diagnosis of the myeloma. The median age of these 71 patients was 70 years and 71.4% were male. MGUS was present in 100% of patients 2 years prior to the diagnosis of MM. At 5 years prior to the diagnosis of MM, 95% had MGUS

while at 8 or more years prior to the diagnosis of MM, 82.4% had a preceding MGUS ***(Landgren et al., 2009).***

The median size of the M protein increased from 0.9 g/dL at 8 years to 1.6 g/dL at 2 years prior to the diagnosis of MM. Approximately one-half of the myeloma patients had a year-by-year increase in M protein until the diagnosis ofMM. The type of M protein was IgG (68%), IgA (21.5%), IgM (1.5%), or biclonal (3%), and 4.7% had light chain MGUS. Thus, this study established that virtually all patients with MM have a preceding MGUS. These findings were confirmed by another study in which 27 of 30 patients with MM had a preceding monoclonal protein. Three patients had no evidence of an M protein; one had only one prediagnostic sample available 9.5 years before the diagnosis ofMM, while the other two patients had IgD myeloma and their most recent prediagnostic samples were 5.3 and 3.3 years prior to the diagnosis of myeloma ***(Weiss et al., 2009).***

The origins of MGUS are likely linked to antigenic stimulation. Studies show that human myeloma cell lines and primary myeloma cells express a broad range of Toll-like receptors which normally help B cells recognize infectious agents and pathogen-associated molecular patterns ***(Bohnhorst et al., 2006).***

TLR-specific ligands cause increased myeloma cell proliferation, survival, and resistance to dexamethasone induced

apoptosis. In addition, there is overexpression of CD126 (interleukin-6 receptor alpha-chain) in MGUS compared to normal plasma cells. Thus abnormal TLR expression and/or overexpression of IL-6 receptors in plasma cells may result in an enhanced response to infection and provide a sustained, autocrine IL-6 dependent, proliferative trigger for plasma cells which cause (or act in concert with) the certain cytogenetic events described below to establish the premalignant MGUS stage ***(Perez-Andres et al., 2005).***

Approximately 50% of MGUS is associated with primary translocations in the clonal plasma cells involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 (IgH translocated MGUS/SMM) ***(Fonseca et al., 2004).***

The most common partner chromosome loci and genes dysregulated in these translocations are: 11q13 (CCND1 [cyclin D1 gene]), 4p16.3 (FGFR-3 and MMSET), 6p21 (CCND3 [cyclin D3 gene]), 16q23 (c-maf), and 20q11 (mafB) Most of the remaining cases of MGUS are associated with hyperdiploidy (IgH non-translocated MGUS) ***(Magrangeas et al., 2005).***

Kristinsson and colleagues describe an important study determining the mortality patterns and causes of death in MGUS patients in comparison to controls. They identified a nation-wide cohort of 4,259 MGUS patients diagnosed from 1986 to 2005 and compared them to 16,151 matched controls. They demonstrated

excess mortality in patients with MGUS. The excess mortality increased with longer follow-up. Younger patients with MGUS had a significantly lower excess mortality rate compared to that of older patients. MGUS patients had an increased risk of dying fromMM, WM, other lymphoproliferative malignancies, other hematologic malignancies, amyloidosis, bacterial infections, ischemic heart disease, other heart disease, other hematologic conditions, liver disease, and renal disease. The major shortcoming of this study is that since MGUS was diagnosed clinically, the causes of death besides plasma cell disorders are likely affected by the reason the patient underwent electrophoresis rather than the presence or absence of MGUS detected on that test. This bias can be overcome only if a study is undertaken on a population-wide basis, or if the deaths in patients who were tested and found negative for MGUS can be used as the control group ***(Kristinsson et al., 2009).***

Nevertheless, they have also found a shorter survival in MGUS patients when compared to the age- and sex-matched normal population. In their report of 241 patients with MGUS, the median survival was 13.7 years, compared to 15.5 years for the USA population using 1930 to 2000 decennial life tables (Figure (1)) ***(Kyle et al., 2004).***

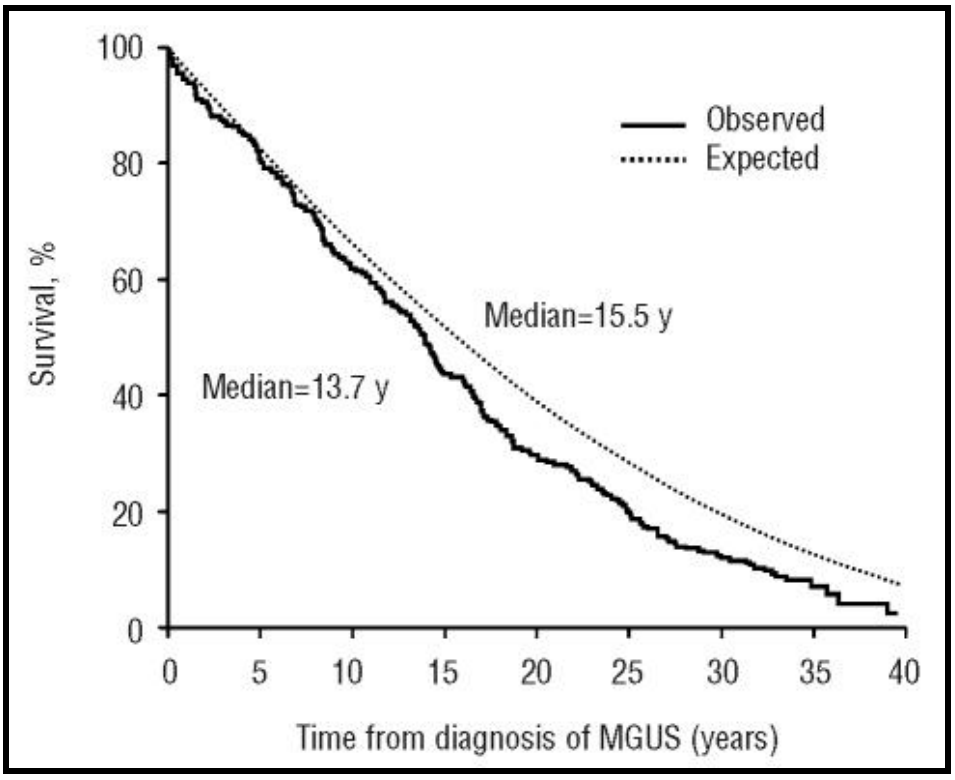

Figure (1): Survival rate of 241 patients with monoclonal gammopathy of undetermined significance compared with expected survival rate of the USA population using 1930–2000 decennial life tables ***(Kyle et al., 2004).***

Each patient was matched to the control population by age, sex, and date of entry. The median survival of their 1,384 patients from Southeastern Minnesota was 8.1 years, compared to the 11.8 years expected for Minnesota residents of matched age and sex. (Figure(2)) ***(Kyle and Rajkumar, 2003).***

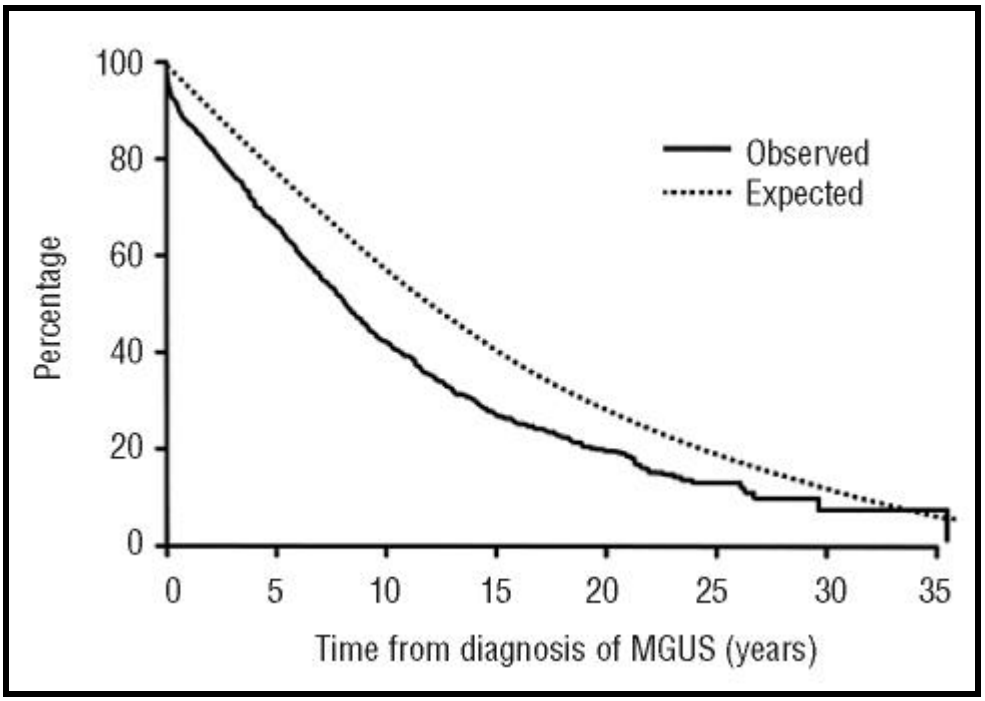

Figure (2): Survival of 1384 patients with monoclonal gammopathy of undetermined significance from South-Eastern Minnesota compared with a normal population (8.1 *vs.*11.8 years, respectively) ***(Kyle and Rajkumar, 2003).***

Van de Poel et al., reported that the long-term survival of 334 patients with MGUS was slightly shorter than the expected survival of age- and sex-adjusted controls. Survival of patients with MGUS has also been reported in cohorts from the Netherlands and from Denmark ***(Van de Poel et al., 1995).***

So,the benign monoclonal gammopathy patient of the past has been shown to be an important element in unlocking the mysteries of the plasma cell dyscrasias – particularly MM. It is well accepted that MGUS patients have an excess risk of developing MM and related plasma cell disorders. It has