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Monoclonal gammopathy of undetermined significance and Waldenström's macroglobulinemia

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A B S T R A C T

Since the initial identification of patients with monoclonal elevation of gamma globulin and associated clinical symptoms in 1944 by Jan Waldenström, several new insights have been gained using a range of approaches. For example, IgM monoclonal gammopathy of undetermined significance and smoldering Waldenström's macroglobulinemia are defined clinical precursor states to symptomatic Waldenström's macroglobulinemia. Epidemiologic studies have established the prevalence of these conditions and the estimated risk of progression to symptomatic disease. Recent molecular studies have identified mutations in the MYD88 and CXCR4 genes as early events in the pathogenesis of IgM MGUS and Waldenström's macroglobulinemia.

In this review we summarize the epidemiologic and molecular features of Waldenström precursor states, the risk stratification and clinical evaluation of these conditions and possible management options. With the advent of more effective and safer treatments for Waldenström's macroglobulinemia, we highlight the possibility of clinical treatment trials targeting patients with smoldering Waldenström's macroglobulinemia.

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a relatively common precursor state especially in individuals over the age of 50 years [1]. MGUS is characterized by serum monoclonal protein measuring less than 3 gm/dL, clonal bone marrow plasma cell infiltrate less than 10% and absence of end organ damage; specifically, no evidence of lytic bone lesions, hypercalcemia, anemia or renal insufficiency [1]. Large population based studies estimate the prevalence of MGUS as approximately 2–3% over the age of 50 years [2,3]. Based on the isotype of the immunoglobulin involved, MGUS could be classified to three major subtypes: non-IgM (i.e. IgG, IgA, IgD or IgE), IgM and light chain subtypes. The non-IgM and light chain subtypes are associated with an increased risk of progression to symptomatic multiple myeloma and the risk of progression is estimated to be approximately 0.5–1% annually [3,4].

IgM Monoclonal gammopathy of undetermined significance

Approximately 10–20% of individuals with MGUS have the IgM subtype, associated with an increased risk of developing Waldenström's macroglobulinemia or other lymphoid malignancies [3,5] (Table 1). Recent studies have also suggested possible racial disparities in the prevalence of IgM MGUS. For instance, in the recently published population based study, the adjusted prevalence of MGUS was noted to be significantly higher in African-American versus Caucasian population (3.7% vs. 2.3%) [5]. However, the prevalence of IgM subtype was lower in the African-American population (2.7% vs. 15.4% of all MGUS identified) [5]. This is consistent with the reported increase in the incidence of Waldenström's macroglobulinemia and related lymphoid malignancies in Caucasians [6].

Dr. Kyle and colleagues at the Mayo Clinic have reported the long term outcomes of individuals with IgM MGUS. Between 1960 and 1994, they identified 213 individuals diagnosed with IgM MGUS and residing in southeastern Minnesota [4]. With relatively long follow-up (1567 person years; median 6.3 years per person) they report an increased incidence of non-Hodgkin lymphoma (17 patients; relative risk, RR: 14.8), Waldenström's macroglobulinemia (6 patients; RR: 262), systemic amyloidosis (3 patients; RR: 16.3) and chronic lymphocytic leukemia (3 patients; RR: 5.7). The relative risk of progression to a lymphoid malignancy was approximately 16-fold higher in these individuals compared to age and gender matched control population. The cumulative incidence of progression was approximately 10% in 5 years and 24% in 15 years. Individuals with IgM MGUS also had a shorter median survival compared to age and gender matched controls (7 vs. 10.8 years) [4].

An independent study from Sweden reported similar outcomes for patients with IgM MGUS [3]. Amongst 728 individuals with MGUS, 116 (16%) had IgM MGUS. With up to 30 years of follow-up, these patients had approximately 15-fold higher risk of progression to lymphoid malignancies, particularly Waldenström's macroglobulinemia.

Smoldering Waldenström's macroglobulinemia

Smoldering Waldenström's macroglobulinemia is a closely related precursor state with a higher risk of progression to symptomatic Waldenström's macroglobulinemia (Table 1). It is defined by a serum

Table 1
Spectrum of IgM related disorders.

	Ig M monoclonal protein	Bone marrow LPL infiltration	End organ damage[a]
Symptomatic Waldenström's macroglobulinemia	Any level	Any level	Yes
Smoldering Waldenström's macroglobulinemia	>3 gm/dL	>10%	No
IgM MGUS	<3 gm/dL	<10%	No

[a] End organ damage includes symptomatic anemia, hyperviscosity, lymphadenopathy, hepatosplenomegaly, cytopenias or constitutional symptoms.