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Monoclonal Gammopathy of Undetermined Significance

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1. Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic plasma cell dyscrasia, present in 3.2% of white people over 50 years of age [1], which converts to multiple myeloma (MM) or related disorders at a rate of just 1% a year [2], an incurable malignancy of plasma cells. While MM is the prototypical monoclonal gammopathy, the most common is MGUS [3].

Monoclonal gammopathies are a heterogeneous group of disorders characterized by the stable or progressive proliferation of an abnormal clone of plasma cells that continue producing antibodies [4]. But because these immunoglobulin proteins are abnormal and monoclonal (identical copies of each other), these offer no protection against infections and can damage the kidney. This monoclonal immunoglobulin is called M-protein. Each basic unit is a monomeric immunoglobulin consisting of two heavy chains of the same class and subclass and two light chains of the same type. The heavy chain classes are G, A, M, D, E (gamma, alpha, mu, delta, epsilon), while the light chain types are kappa (κ) and lambda (λ).

Monoclonal gammopathies are recognized on serum protein electrophoresis demonstrating a band of migration in the beta or gamma region [5]. When a band is seen on serum protein electrophoresis, immunofixation electrophoresis should be performed. Immunofixation electrophoresis is the gold standard and should be performed to confirm the presence of an M-protein and to distinguish its heavy chain and light chain type [6].

In 1952, Waldeström [7] initially reported finding an M-protein without evidence of malignant disorder, and named the condition "essential hypergammaglobulinemia". For some time, this

condition was also referred to as "benign monoclonal gammopathy". However, Kyle recognized that some patients with MGUS could progress to MM, Waldeström macroglobulinemia, light chain amyloidosis, or related disorders. Thus, Kyle coined the term MGUS in 1978 [8]. In 2003, MGUS is defined by serum M-protein concentration less than 3 g/dL, the bone marrow clonal plasma cell less than 10%, with no evidence of other B-cell proliferation disorders [9].

The objective of this chapter is to describe new concepts and advances concerning the diagnosis, classification, management of patient, risk factors for malignant transformation and new preventive strategies of progression of MGUS to malignant conditions.

2. Prevalence

As mentioned above, MGUS is the most common plasma cell disorders and is a potential precursor of MM. At the Mayo Clinic during 2005, 51% of patients with a monoclonal gammopathy (n=1,510) had MGUS, 18% MM, 11% amyloidosis, 3% Waldeström macroglobulinemia and 17% other diseases [3].

In 1972, Kyle et al [10] collected serum from 1,200 residents (≥50 y) of Thief River Falls of Minnesota; M-proteins were detected in 15 people, 1.7% men and 0.9% women of the surveyed population (Table 1). In 2006, Kyle et al [1] reported variability in the prevalence of MGUS from a normal population in community practice [11, 12] or in hospitals; data was obtained from studies carried out between 1963 and 2002. It is suggested that this variability might be due to that some studies lacked a geographically defined population in which testing could be performed during a specified period, and that screening methods used in many previous studies are less sensitive than current techniques. To overcome these limitations, Kyle et al [1] used sensitive laboratory procedures to determine the prevalence of MGUS in a large population (n=21,463) in a well-defined geographic area (Table 1): sample of persons aged ≥50 years residing in Olmsted Country (Minnesota, USA). MGUS was found in 3.2% of people in their 5th decade, 5.3% in their 7th decade and 7.5% in over 85 years old (350/9469 men and 344/11,994 women) [1]. Axelsson et al [13] also reported that MGUS is more prevalent in men (1.9%) than in women (1.3%).

The incidence in the population aged 70 years reaches 3% in Caucasian population [4] and 0.7% in Mexican mestizos [14]. The prevalence of MGUS in African Americans was 3-fold higher than in white male veterans, among 4 million African American and white male veterans admitted to Veterans Affairs, between 1980 and 1996 [15] (Table 1). The age-adjusted prevalence of MGUS was 1.97-fold higher in Ghanaian men compared with white men (50-74 y) [16]. Later, they reported the risk of MGUS between white and black male United States veterans could be associated with prior autoimmune, infectious, inflammatory, and allergic disorders; they concluded that various types of immune-mediated conditions might act as triggers for MM/MGUS development [17]. Recently, a disparity in the prevalence, pathogenesis and progression of MGUS between blacks and whites [18] has been reported.

Site [References]	Type Study (Length)	Test Identify M-protein	N° of Persons Studied (Age, y)	Prevalence % (Age, y); Incidence or Cases	M-protein		
					IgG % n/MGUS	IgA % n/MGUS	IgM % n/MGUS
Minnesota, USA [10]	PB (<1 mo)	CAE IE	1,200 (≥50)	1.25 % (≥50) 2.8 % (≥70)	73.3 % 11/15	6.7% 1/15	20.0% 3/15
Finistere, France [11]	Health CP (1 y)	CAE IE	30,279 (≥30) 17,968 (≥50)	0.2 % (all) 1.7 % (≥50)	71.7% 43/60	6.6% 4/60	21.7% 13/60
North Carolina, USA [12]	PB (NA)	AGE IFE	1,732 (≥70)	6.1% total 8.4/3.8% blacks/whites	NA/106	NA/106	NA/106
Iceland [20]	RCS (22 y)	CAE AGE	Population Iceland (20-104)	11/100,000 (M) 9/100,000 (F)	55.0%	13.0%	32.0%
Hospital, Japan [21]	HCS-BS (16 y)	CAE IE	6,737 (45-85)	0.93% 2.0% (≥70)	55.8%	41.6%	-
Minnesota, USA [1]	PB (6 y)	AGE IFE	21,463 (≥50)	3.2 % (≥50) 3.7/2.9% (M/F)	68.9% NA/694	10.8% NA/694	17.2% NA/694
142 VA hospitals [15]	RS-IHR (16 y)	NA	3,997,815(≥18)	0.05% total; 0.09% blacks 0.04% whites	NA/2,046	NA/2,046	NA/2,046
LHNC, Japan [22]	RS-BS (15.5 y)	CAE IE	52,781 (≥42)	2.1% (all) 4.4 % (≥80)	73.6% NA/1,088	17.7% NA/1,088	7.5% NA/1,088
1 hospital, Chile [23]	RS	AGE IFE	MGUS: 17 (28-96)	NA 11/6 (M/F)	59.0% 10/17	24.0% 4/17	18.0% 3/17
Bangkok, Thailand [24]	SH (6 mo)	HRGE AGE	3,260 (50-93)	2.3% 38/46% (M/F)	64% 48/75	21.3% 16/75	--
Seongnam, Korean [25]	KL (1 y)	SPEP IFE	1,118 (65-97)	3.1% 3.8/2.5% (M/F)	29% 6/21	43% 9/21	19% 4/21
Germany [26]	PB-HNR	SPEP IFE	4,702 (45-75)	3.5% 4.4/2.7% (M/F)	59% 97/165	17% 28/165	17% 28/165

AGE: Agarose gel electrophoresis; **CAE**: Cellulose acetate electrophoresis; **CP:** Control prevalence; **HCS-PS:** Hospital cohort study- atomic bomb survivors; **HRGE:** High-resolution gel electrophoresis; **IFE:** Immunofixation; **IE**: Immunoelectrophoresis; **KL:** After scheduled tests for the Korean longitudinal study on health and aging; **LHNC:** Local hospital Nagasaki City**; M/F:** Males/females; **NA:** No available; **PB:** Population based; **PB-HNR:** Population-based Heinz Nixdorf Recall study; **RCS:** Retrospective cohort study; **RS:** Retrospective study; **RS-BS:** Retrospective study of date base of atomic bomb survivors; **RS-IHR:** Retrospective study of inpatient hospitalization records; **SH:** Cross-sectional survey of healthy; **SPEP:** Standard serum electrophoresis; **VA:** Veterans Affairs.

Table 1. Studies of epidemiology of MGUS

In 2010, Wadhera and Rajkumar [19] on the basis of a systematic review of prevalence of MGUS selected 14 of 460 articles, which met the inclusion criteria for their review [10, 12, 15, 16, 20-22] (Table 1). They discussed study types, method sensibility and availability to detect M-protein and diagnostic criteria. They conclude that the prevalence increases with age and is affected by race, sex, among other factors. Further studies of prevalence are shown in Table 1 [23-26].

One long-term research studied a population-based of 1,384 patients with MGUS from the 11 counties of southeastern Minnesota who were evaluated from 1960 to 1994 [2]. These patients were observed for a total of 11,009 person-years. Of the identified MGUS, 115 progressed to MM or related disorders. At 10 years, 10% had progressed; 20 years, 21% had progressed; and at 25 years, 26% had progressed. The conclusion of these authors is that the risk of progression is about 1% per year. In 2003, a study reported that relative risk of progression was 16-fold higher in the patients with IgM MGUS than in the white population of the Iowa Surveillance [27]. Furthermore, risk for progression to lymphoma or a related disorder at 10 years after the diagnosis of MGUS was 14% with an initial M-protein concentration of 0.5 g/dL or less, 26% with 1.5 g/dL, 34% for 2.0 g/dL, and 41% for more than 2.5 g/dL [27]. Risk factors associated with the progression will be discussed later in this chapter.

3. Diagnosis and classification of patient with MGUS

The UK Myeloma Forum and the Nordic Myeloma Study Group have proposed guidelines for the effective clinical investigation of patients with M-proteins and management of patients with MGUS [28]. These guidelines are almost entirely based on expert consensus opinion. They were searched by MEDLINE and EMBASE systematically for publications from 1950 to October 2008. They suggest that screening normal populations for M-protein for clinical purposes are not recommended. It was suggested that serum protein electrophoresis should be performed if there is clinical suspicion of an M-protein or when the abnormal test results (erythrocyte sedimentation rate >30 mm/h or plasma viscosity; unexplained anemia, hyper-calcemia or renal failure; raised total protein/globulin or immunoglobulins; reduction of one or more immunoglobulin class levels).

The UK Myeloma Forum and the Nordic Myeloma Study Group guidelines specifically state that there is no evidence supporting the use of serum free light chain in monitoring patients [28]. By contrast, the International Myeloma Working Group members suggest that serum free light chain analysis may be a useful adjunctive test in monitoring patients with MGUS [29-33]. The ratio of κ/λ is critical to the interpretation, because an abnormal serum free light chain ratio should only be present in the context of a plasma cell dyscrasia with severe renal failure or other B-cell lymphoproliferative disorders [34]. It is important to note that serum free light chain analysis by immunoassay is much more sensitive than the serum protein electrophoresis methodology [35].

In 2010, International Myeloma Working Group has recommended a new classification of MGUS [36]; each type must meet all the criteria set out: Non-IgM (IgG or IgA) MGUS with serum M-protein <3 g/dL, clonal bone marrow plasma cells <10%, absence of end-organ

damage, such as CRAB (hypercalcemia, renal insufficiency, anemia and bone lesions); IgM MGUS with serum M-protein <3 g/dL, clonal bone marrow lymphoplasmacytic cells <10%, absence of end-organ damage; and light chain-MGUS with abnormal free light chain ratio <0.26 or >1.65, increased level of the appropriate involved light chain, increased κ free light chain in patients with ratio >1.65 and increased λ free light chain in patients with ratio <0.26, no immunoglobulin heavy chain expression on immunofixation, clonal bone marrow plasma cells <10%, and absence of end-organ damage, such as CRAB [19, 36]. Each clinical type is characterized by unique intermediate stages and progression events. The intermediate stages with high risk of progression are [36]: (i) smoldering MM (SMM: IgG or IgA M-protein ≥3 g/dL, and/or clonal bone marrow plasma cells ≥10%, and absence of end-organ damage, CRAB); (ii) smoldering Waldenström macroglobulinemia (IgM M-protein ≥3 g/dL and/or clonal bone marrow lymphoplasmacytic infiltration ≥10%, no evidence of anemia constitutional symptoms); and (iii) idiopathic Bence Jones proteinuria (urinary M-protein on urine protein electrophoresis ≥500 mg/24 h and/or clonal bone marrow plasma cells ≥10%, no immunoglobulin heavy chain expression on immunofixation, absence of end-organ damage, CRAB).

4. Risk factors for malignant transformation of MGUS

Risk factors for transformation of MGUS to malignant condition have been analyzed in several studies. An abnormal serum free light chain ratio (κ/λ), non-IgG MGUS, and a high serum M protein level (≥1.5 g/dL) are three major risk factors for the progression of MGUS to myeloma [36].

Based on the clinical markers still available, two independent studies were able to establish predictive risk models from MGUS to MM for each clinical type of MGUS. The first model, proposed by a group at the Mayo Clinic identifies three main risk factors for progression: serum M-protein >1.5 g/dL, IgG subtype and normal free light chain ratio. The probability of progression of MGUS to malignant monoclonal gammopathy is 1% per year, with an estimated risk of progression of 34% over 20 years [37]. At 20 years of follow-up, absolute risk of progression for MGUS patients with 0, 1, 2, and 3 risk factors are 5%, 21%, 37%, and 58%, respectively [29].

Immunophenotyping is an attractive technique to potentially identify high levels of malignant plasma cells among normal plasma cells [38] and for the differential diagnosis between MGUS and MM [39]. The second model, proposed by a Spanish group, introduces a novel prognostic criterion for MGUS. This group has established a multiparameter flow cytometry as a tool to identify aberrant plasma cell populations: CD38+, CD19-, CD45-, CD56+ [40]. They defined two factors: (1) a plasma cell/normal bone marrow plasma cell ratio >95% associated with higher risk of progression, and (2) DNA aneuploidy. Free progression survival at 5 years for MGUS patients with 0, 1, and 2 risk factors is 2%, 10%, and 46%, respectively.

Both models present advantages and disadvantages with regard to the risk stratification of patients with MGUS [41]. The Mayo Clinical model may be useful in routine clinical practice, but the disadvantages of the model are its poor discrimination of the risk of progression

between groups. On the other hand, the Salamanca model is a superior model, in particular, to identify a truly high-risk MGUS population; however, its main disadvantages are invasiveness (it requires a bone marrow aspirate), technical complexity and high cost.

The biological events related to progression from normal plasma cells to MM precursor disease and to MM involve many overlapping oncogenic steps that differently affect each individual [42]. Several authors discuss the very early and partially overlapping molecular pathogenic events that are shared by MGUS, and how they are associated to progression at the MGUS to MM transition [43-45].

5. Cytogenetic studies on MGUS and SMM

MGUS, SMM and MM present common chromosomal abnormalities [46-49] whose prevalence and relative association between these diagnostic groups have been controversial for years. The development of new techniques and methodologies has helped to define new biomarkers and elucidate the pathogenetic mechanisms of progression, characterized as a multistep process from the precursor state to myeloma.

The first step in the pathogenesis is likely an abnormal response to antigenic stimulation, mediated possibly by aberrant expression of toll-like receptors and overexpression of interleukin (IL) 6 receptors and IL-1β. This then results in the development of primary cytogenetic abnormalities, either hyperdiploidy or immunoglobulin heavy chain translocations [36]. Hyperdiploid tumors, which include about 50% of MM tumors, often have multiple trisomies involving chromosomes 3, 5, 7, 9, 11, 15, 19, and 21; also, a substantially lower prevalence of immunoglobulin heavy chain translocations and monosomy of chromosome 13 compared with nonhyperdiploid tumors. Trisomies of these same chromosomes also occur in premalignant MGUS tumors [47].

It has been well established that each translocation subgroup found in MM tumors is associated with deregulation of a D group cyclin either directly, such as occurs with the t(11;14) (cyclin D1) and t(6;14) (cyclin D3) or indirectly, such as occurs with the t(4;14) or in the MAF translocation group [47]. All these translocations have also been reported in MGUS (Table 2).

The first studies that showed structural chromosomal changes in MGUS and performed fluorescence *in situ* hybridization experiments (FISH) found 14q32 and 13q14 abnormalities [51, 52]. Subsequent studies have determined that approximately 50% of SMM show primary translocations involving the immunoglobulin heavy chain locus leading to the dysregulation of oncogenes including the Cyclin D, FGFR3/MMSET and MAF genes [46, 48, 53] (see Table 2). There is evidence of an immunoglobulin light chain-λ translocation in MGUS associated with a prevalence of 10% in MGUS/SMM [53].

Ross et al [55] found that cases characterized by t(4;14), t(14;16), particularly the t(14;20), can be stable as either MGUS or SMM for years before progression occurs. It has been shown that t(4;14), t(14;16) and t(14;20) translocations are associated with a poor prognosis in MM

Translocation (Prevalence %) [References]	Group	Deregulated Gene	Cell Level Consequence
IgH translocated MGUS (50%) [50]			
t(11;14)(q13;q32) (15%-25% of MGUS/SMM patients) [50-53]	D group cyclin Directly	CCND1	Enhance cyclin D1 (normally B-cells express cyclin D2 and cyclin D3 but not cyclin D1)
t(6;14)(p21;q32) (1% of MGUS/SMM patients) [50]	D group cyclin Directly	CCND3	Enhance cyclin D3
t(4;14)(p16;q32) (2%-5% of MGUS patients) (13% of SMM patients) [48, 52-54]	D group cyclin Indirectly	FGFR-3 and MMSET	Enhance cyclin D2
t(14;16)(q32;q23) (3%-5% of MGUS/SMM patients) [53, 55]	MAF translocation group	c-MAF upregulation	Enhance cyclin D2
t(14;20)(q32;q11) (5% of MGUS patients) (0%-1.5% of SMM patients) [50, 55]	MAF translocation group	MAFB upregulation	Enhance cyclin D2

MGUS: Monoclonal gammopathy of undetermined significance; **SMM:** Smoldering multiple myeloma

Table 2. Translocations into the immunoglobulin heavy chain locus in MGUS and SMM patients

(1,860 studied patients). The t(14;20) patients had a short median survival of only 14.4 months [50]. It has been determined that these three translocations produce cyclin D2 enhancement (Table 2).

Using interphase FISH, Chiecchio et al [50] performed a study to evaluate chromosome 13 deletion (delta 13), deletion of TP53 (17p13), ploidy status and immunoglobulin heavy chain translocations. They found that 50% of MGUS patients carried one of the primary immunoglobulin heavy chain translocations and the remaining patients displayed a hyperdiploid karyotype. Thus 72/189 (42%) MGUS, 70/127 (63%) SMM, and 223/338 (57%) of MM cases were hyperdiploid. When the individual incidences of the specific translocations were compared, only t(4;14) was significantly less frequent in MGUS. The authors propose that ploidy status and immunoglobulin heavy chain rearrangements were early events delineating different pathogenic pathways [50]. The study revealed a significantly lower frequency of delta 13 in the pre-malignant conditions than in MM. Delta 13 was rare in MGUS (25%) and SMM (34%) compared to MM (47%).Translocations directly involve cyclin D genes (CCND1 and CCND3) suggesting a possible role of delta 13 in the progression of the disease, specifically in these genetic sub-groups [50]. In MGUS, the greatest variation in the proportion of abnormal plasma cells carrying the abnormality was seen for delta 13 and 16q23 deletion. The presence and time of occurrence of delta 13 depend on the presence of specific concurrent abnormalities: earlier

when t(4;14) or t(14;16) was present, later with t(14;20), and even later with t(11;14) or t(6;14).This data suggests a possible role of delta 13 in the transition from MGUS to MM specifically in cases with t(11;14) or t(6;14). Chromosome 13 deletion on its own probably does not affect prognosis [50].

We have treated previously in this chapter, that MGUS progresses to MM at annual frequency of 1% [2], however little is known about the proportion of patients whose MM has evolved from this precursor condition. Zhan F et al [56] developed a gene-expression profiling study in which 52 genes differentially expressed in MGUS and MM identifying and validating a MGUS-like MM with favorable clinical features and longer survival.

Point mutations, such as N-RAS, K-RAS, MYC up-regulation, and gain or loss of chromosome 1q or 1p, also seem to correlate with disease progression from myeloma precursor disease, MGUS and SMM [57]. Rasmussen et al [58] found a high prevalence of activating RAS mutations in MM (31%) compared with MGUS (5%) and suggest that these mutations may facilitate the transition from MGUS to MM in a subset of patients. Only N-RAS mutation was found in MGUS. At present, RAS mutations are the major genetic difference between MGUS and MM [43].

In a case report, Chiecchio et al [59] describe the clinicopathological and genetic findings of a young patient initially diagnosed with SMM: loss of 1p and a rearrangement of MYC were first observed in a small population of plasma cells one year prior to the clinical diagnosis of MM, but these subclones increased rapidly in size to become the major population suggesting that they were directly involved in the transformation [59].

MicroRNA is a novel class of short non-coding RNA molecules regulating a wide range of cellular functions through translational repression of their target genes. Recently, epigenetic dysregulation of tumor-suppressor microRNA genes by promoter DNA methylation has been implicated in human cancers, including MM [60]. It has been reported that MGUS and MM patients seem to upregulate miR-21, miR-106b, miR-181a, and miR-181b; which are microRNA involved in B-cell and T-cell lymphocyte differentiation as well as oncogene regulation [61]. Recently, Jones et al [62] have developed a biomarker signature using microRNAs extracted from serum, which has potential as a diagnostic and prognostic tool for MM. The combination of miR-1246 and miR-1308 can distinguish MGUS from myeloma patients [62].

In the progression process to malignant condition it also seems to be important the proportion of clonal plasma cell with specific genetic abnormalities in every diagnostic group. In fact, López-Corral et al [63] observed a significant difference in MGUS compared with SMM, and in SMM compared with MM, suggesting that the progression from MGUS to SMM and eventually to MM involves a clonal expansion of genetically abnormal plasma cell. This result was found for immunoglobulin heavy chain translocations, 13q and 17p deletions, and 1q gains. In other recent study, López-Corral et al [49] analyzed the genomic characteristics by FISH, Single-nucleotide polymorphism arrays and gene expression profile finding that the overexpression of four SNORD genes (SNORD25, SNORD27, SNORD30 and SNORD31) was correlated with shorter time progression to symptomatic MM. However, they failed to find chromosomal lesions associated to risk of progression, observing an increase in the proportion

of clonal plasma cells carrying a given abnormality supporting the hypothesis that the number of genetically abnormal plasma cell increases from high-risk SMM to active MM [49]. In a later study López-Corral et al [64] have performed for the first time a comprehensive high-resolution analysis of genomic imbalances by high-density 6.0 S SNP-array in 20 MGUS, 20 SMM and 34 MM patients to search for the genetic lesions that may be involved in the transformation from MGUS to MM. Their results showed a progressive increase in the incidence of copy number abnormalities from MGUS to SMM and to MM. The study shows for the first time the different copy number and loss of heterozygosity profiles present at three stages of monoclonal gammopathy evolution: MGUS, SMM and MM. There were significantly more copy number alterations in MM than in MGUS patients, values for SMM being intermediate [64].

Taking into account that the majority of MM plasma cell are quiescent, it has been suggested that the growth of the tumor is restricted to a specialized subpopulation of cells [43]. In this sense, the bone marrow microenvironment plays an essential role in the pathogenesis of MM. The bone marrow microenvironment in which MGUS and MM cells live is composed of extracellular matrix and different types of cells, e.g., stromal cells, osteoclasts, osteoblasts, immune cells (T lymphocytes, dendritic cells), other hematopoietic, cells and their precursors, and vascular endothelial cells. Reciprocal positive and negative interactions among these cells are mediated by a variety of adhesion molecules, cytokines, and receptors [65]. MAF translocations dysregulate expression of a MAF transcription factor that causes increased expression of many genes, including CCND2 and adhesion molecules that are thought to enhance the ability of the tumor cell to interact with the bone marrow microenvironment [66].

In summary, it has been proposed that the pathogenesis of MGUS and MM can be considered as occurring in three phases [6]. First, partially overlapping genetic events common to MGUS and MM include at a minimum primary immunoglobulin heavy chain translocations, hyperdiploidy, and del13 that lead directly or indirectly to dysregulation of a CCND gene; second, the transition from MGUS to MM is associated with increased MYC expression and sometimes K-RAS mutations, but can also include del13 in t(11;14) tumors; third, additional progression of the MM tumor seems to be associated with other events. For example, increased proliferation and genomic instability, and decreased dependence on the bone marrow microenvironment, sometimes including extramedullary spread of disease, can be associated with late MYC rearrangements that often involve an immunoglobulin locus, activating mutations of the nuclear factor-κB pathway, deletion or mutation of TP53, and inactivation of p18INK4c or RB [65] (see Fig. 1).

6. Clinical management

As mentioned above, the UK Myeloma Forum and the Nordic Myeloma Study Group have proposed guidelines for the management of MGUS [28]. They suggest that is essential that patients should be monitored not only by laboratory testing but also clinically. Low risk patients (serum IgG <1.5 g/dL; IgA or IgM <1.0 g/dL; normal free light chain ratio in the absence of symptoms such as anemia or renal dysfunction) can be monitored in the primary-care setting
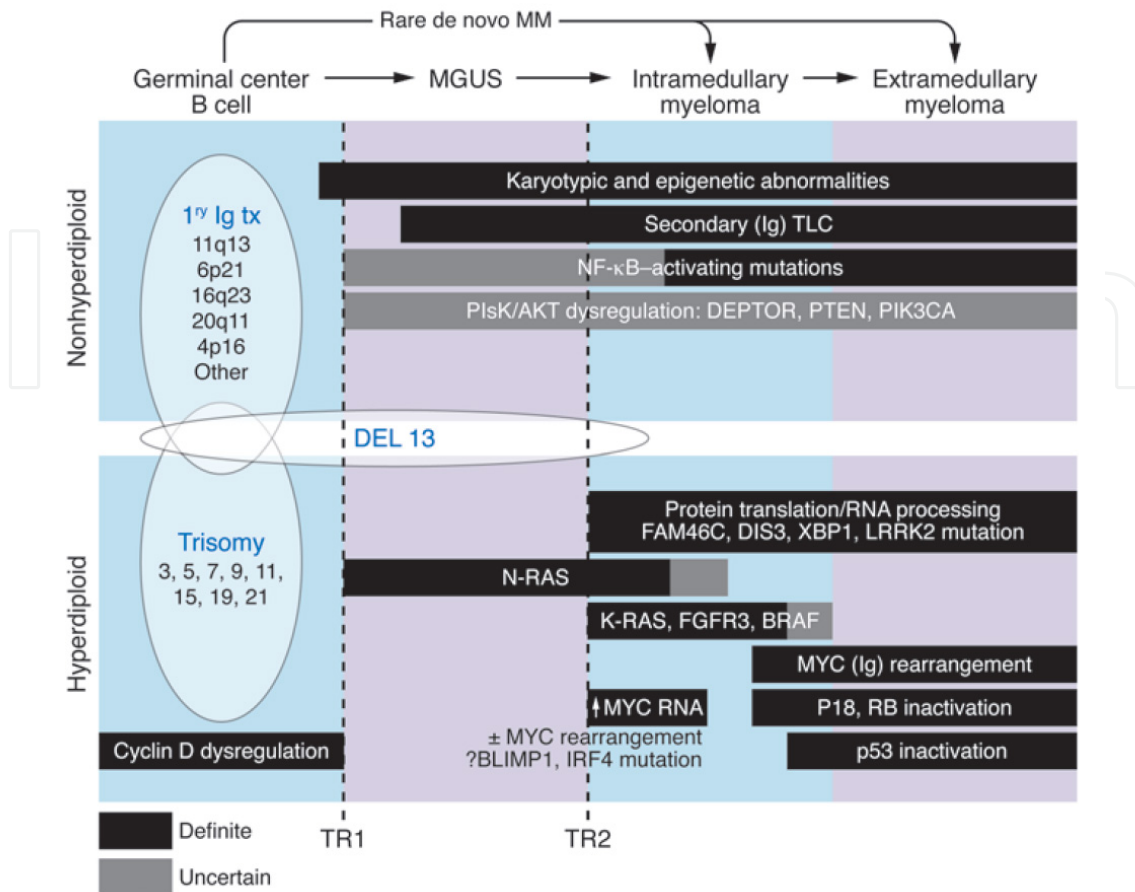
Figure 1. Model for molecular pathogenesis of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). TR1, the initial transition to a recognizable tumor involves two mostly non-overlapping pathways (IgH translocations versus multiple trisomies) that include primary events associated with dysregulated cyclin D expression in MGUS and MM. TR2, the transition from MGUS to MM is associated with increase MYC expression and sometimes with activating mutations of K-RAS or chromosome 13 deletion. Early and late progression events for symptomatic MM tumors are shown. Reproduced with permission from Kuehl WM and Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. J Clin Invest. 2012;122(10):3456-63. doi:10.1172/JCI61188. Copyright from the American Society for Clinical Investigation.

at intervals of 3-4 months initially for the first year and then lengthened to 6-12 months based on the patient`s clinical history, laboratory results and comorbid conditions. Should be checked for serum protein electrophoresis, complete blood count, calcium, and serum creatinine every 6 months and if they are stable, every 2 to 6 years. There is also an alternative strategy suggesting that screening should be performed only if there is an increase in symptoms associated with MM. International Myeloma Working Group members suggest that the patients with low risk-MGUS should be followed during 6 months after the diagnosis of MGUS [32]. On the other hand, they specified that a bone marrow examination should be required if the patients had any CRAB features.

UK Myeloma Forum and the Nordic Myeloma Study Group recommend that patients with high-risk MGUS (IgG ≥1.5 g/dL; IgA or IgM >1.0 g/dL; IgD or IgE at any level) should be referred to a hematology specialist 3-4 times per year as a minimum [28]. The

recommended tests for monitoring include serum protein electrophoresis, serum total immunoglobulin, complete blood count, creatinine, urea, electrolytes and serum calcium. In addition, it should be evaluated using bone marrow cytogenetic and FISH with bone imaging studies. Nevertheless, it is important to highlight that sometimes it will be necessary to perform Magnetic Resonance Imaging or Positron Emission Tomography-Computed Tomography, instead of traditional x-rays. Patients with unexplained anemia or kidney failure should be evaluated with a full bone scan that also include cytogenetic and FISH. Korde et al [57] reported that is critical to recognize that in a disease such as MM, where defining criteria rely on the presence or absence of end-organ damage, diagnosis is only as good as the tools and technology able to detect end-organ damage. For instance, in SMM or high-risk MGUS patients suspicious to harbor bone disease, imaging evaluation may be better served by obtaining magnetic resonance imaging or Positron Emission Tomography-Computed Tomography rather than traditional skeletal surveys. International Myeloma Working Group members recommend for intermediate-risk and high-risk MGUS patients should have a bone marrow aspirate and biopsy with both conventional cytogenetics and FISH [32]. If available, a plasma cell labeling index and a search for circulating plasma cells in the peripheral blood using flow cytometry are useful. Patients with IgM isotype should have a computational tomography scan of the abdomen since asymptomatic retroperitoneal lymph nodes may be present. If there is evidence of MM or Waldeström macroglobulinemia, lactate dehydrogenase, 2-microglobulin, and C-reactive protein levels should be measured. If the results of these tests are satisfactory, International Myeloma Working Group recommend patients should be followed with serum protein electrophoresis and complete blood cell count in 6 months and then annually for life [32].

7. Management

In clinical practice, patients with MGUS are followed clinically without treatment until progression. However, the existence of easily identifiable precursor states represents an opportunity for chemoprevention [67]. However, it must be weighed that benefits achieved by treating a precursor state is greater than a potential for therapeutic toxicity. Recently, Korde et al [57] revised early treatment strategies for MGUS and SMM.

Bhattacharyya et al [68] reported a clinic case of IgM-MGUS associated with cryoglobulinemia and cold agglutinin disease, which was treated with immunotherapy and was successful (Table 3). Immunochemotherapy, consisting of rituximab (375 mg/m2, day 1), fludarabine (25 mg/m2, days 2-4), and cyclophosphamide (250 mg/m2, days 2-4), was administered every 4 weeks up to three times as a first-line treatment followed by three cycles of monthly rituximab treatment. Extensive skin lesions with livedo reticularis entirely disappeared prior to initiation of the second cycle in association with the declined serum level of IgM.

Pepe et al [69] studied 100 patients affected by MGUS, grouped according to the presence (group A, 50 patients) or absence (group B) of vertebral fractures and/or osteoporosis. Group A was treated with alendronate (70 mg/weekly) plus calcium and cholecalciferol for 18

Drug [References]	Treatment scheme	Nº of patients (age or study/control)	Benefit	Observations
Zoledronic acid [70]	4 mg, i.v. at 0, 6, and 12 months	54 MGUS and osteopenia or osteoporosis (50-91 years; median=67 years)	Reducing fractures.	48 patients completed the study. Some patients showed adverse effects. Progression of MGUS does not diminish with time.
Alendronate plus calcium and cholecalciferol *vs.* calcium and cholecalciferol [69]	70 mg/weekly, at 18 months	100 MGUS With presence or absence (control) vertebral fractures and/or osteoporosis (50/50)	Reducing fractures.	8 patients developed MM 12 patients did not want to take the drugs.
Rituximab, fludarabine, and cyclophosphamide [68]	Every 4 weeks up to three times followed by three cycles of monthly rituximab treatment	1 MGUS associated with cryoglobulinemia and cold agglutinin disease	Decreases M-protein and skin lesions disappeared.	NA
Curcumin vs. placebo [73]	4 g/day oral	26 MGUS (17/9)	Decreases bone resorption and M-protein (12-30%) of patients with M-protein >20 g/L	NA
Curcumin vs. placebo [74]	4 g/day and an open-label 8 g curcumin extension study, oral, at 3 months	19 MGUS 17 SMM (12/13)	Decreasing free light chain and marker of bone resorption.	Curcumin may benefit some but not all patients with MGUS and SMM.

MGUS: Monoclonal gammopathy of undetermined significance; **SMM:** Smoldering multiple myeloma; **NA:** Not available.

Table 3. Therapy on patients with MGUS

months, and group B was treated with calcium and cholecalciferol. Treatment with alendronate could lead to a significant reduction in fracture risk in MGUS patients with skeletal fragility. During the whole period of investigation, eight patients in group A developed MM and therefore were not able to continue the study. A further 12 patients included in group A did not want to take the drugs prescribed. Additionally, the author indicated that this study has some limitations, mainly because of the lack of a real control group (longitudinally followed for the entire observation period) and the lack of morphometric evaluation of vertebral fractures at 18 months. Another similar study was administered zoledronic acid to

54 patients with MGUS and osteopenia or osteoporosis [70]. They also demonstrated that increase bone mineral density in patients with bone loss with the theoretical added benefit of reducing fractures although it was not observed that the progression can be delayed or prevented.

There are two ongoing studies, in the first, the aim is to assess whether omega-3 fatty acids reduce activated NF-κB levels in peripheral blood lymphocytes [71]. Omega-3 supplementation will be initiated at three 1250 mg capsules daily for the first month. If dose is well tolerated, it will be increased to six 1250 mg capsules daily for 30 days and finally to nine 1250 mg capsules daily. Treatment period is 12 months (study design nonrandomized). No study results posted on clinicaltrials.gov [71]. In the second study, the aim is to test whether green tea extract reduces the M-protein concentration [72]. Patients receive oral green tea catechin extract (Polyphenon E) daily on days 1-28. Treatment repeats every 28 days for up to 6 courses in the absence of disease progression or unacceptable toxicity. No study results posted on clinical-trials.gov [72].

Golombick et al [73] investigated the effect of curcumin on plasma cells and osteoclasts in patients with MGUS (see Table 3). Twenty-six patients with MGUS were randomized into two groups (single-blind, randomized, crossover pilot). The pilot study found that curcumin may decrease both serum M-protein (in patients with levels of >20 g/L) and urinary N-telopeptide of type I collagen bone turnover marker in patients with MGUS. Recently, Golombick et al [74] performed a randomized, double-blind placebo-controlled crossover 4 g curcumin study and an open-label extension study using an 8 g curcumin. 19 MGUS and 17 SMM were randomized into two groups: one received 4 g curcumin and the other 4 g placebo, crossing over at 3 months. 25 patients completed the 4 g crossover study and 18 the 8 g extension study. In some patients curcumin therapy decreased the free light-chain ratio and uDPYD (a marker of bone resorption).

Curcumin is the most active component in *Curcuma longa* or turmeric (tropical plant native to southern and southeastern tropical Asia). Curcumin has been shown to downregulate IL-6 and nuclear factor-κB; to inhibit osteoclastogenesis and to reduce bone turnover; suppresses proliferation and induces apoptosis in MM cells [75] and inhibits osteoclastogenesis through the suppression of RANKL signaling [76]. Nevertheless, it is known that curcumin inhibits IL-12 production in dendritic cells, thereby dampening the Th1 response [77]. This suggests that may have an immunosuppressive effect. However, Rajkumar [78] indicated that finding reported by Golombick [74] is a modest decrease in free light chain levels by 25-50% in one quarter of the patients, reason why he disagrees with curcumin as a preventive or therapeutic strategy in MGUS (Table 3). Rajkumar also indicated that using risk stratification model approximately 50% of all MGUS patients are considered low-risk MGUS, and have a lifetime risk of progression of only 2%. Therefore, he recommends that focus should be put on preventive strategies in patients with high-risk SMM.

There is an increased interest in identifying biomarkers that can predict patients who will inevitably progress to symptomatic MM. These include genetic and/or epigenetic targets and microenvironment and/or its interaction with tumor cells, which may change the future of

disease progression [65]. Dynamic changes in tumor and microenvironment, cell immunophenotype, mRNA and protein expression, should offer insight into disease progression [57, 78].

8. Conclusion

In conclusion, it is crucial to follow up cases of MGUS carefully, including their systematic recording as a fundamental contribution to understand the evolution of this pathology and its malignant transformation process. This will be critical to develop better biomarkers that contribute to understand the evolution and malignant transformation of MGUS. These efforts should lead to the development of new, more effective management and treatment strategies.

Abbreviations

CRAB	Hypercalcemia, renal insufficiency, anemia and bone lesions
FISH	Fluorescence *in situ* hybridization
IL	interleukin
κ	Kappa
λ	Lambda
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
M-protein	Monoclonal protein
NF-κB	Nuclear factor-κB
SMM	Smoldering multiple myeloma

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References

[1] Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, Dispenzieri A, Katzmann JA, Melton LJ 3rd. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354(13):1362-69.

[2] Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, Melton LJ 3rd. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002;21;346(8):564-69.

[3] Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance. Br J Haematol. 2006;134(6):573-89.

[4] Kyle RA. The monoclonal gammopathies. Clin Chem. 1994;40(11 Pt 2):2154-61.

[5] Kyle RA. Sequence of testing for monoclonal gammopathies. Arch Pathol Lab Med. 1999;123(2):114-18.

[6] Attaelmannan M, Stanley L. Understanding and identifying monoclonal gammopathies. Clin Chem. 2000;46(8):1230-38.

[7] Waldeström J. Studies on conditions associated with disturbed gamma globulin formation (gammopathies). Harvey Lect. 1960-1961;56:211-31.

[8] Kyle, RA. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. Am J Med. 1978; 64(5):814-26.

[9] International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121(5):749-57.

[10] Kyle RA, Finkelstein S, Elveback LR, Kurland LT. Incidence of monoclonal proteins in a Minnesota community with a cluster of multiple myeloma. Blood. 1972;40(5): 719-24.

[11] Saleun JP, Vicariot M, Deroff P, Morin JF. Monoclonal gammopathies in the adult population of Finistere, France. J Clin Pathol. 1982;35(1):63-68.

[12] Cohen, HJ, Crawford, J, Rao, MK, Pieper, CF, Currie, MS. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the enderly. Am J Med. 1998;104(5):439-44.

[13] Axelsson U, Bachmann R, Hällén J. Frequency of pathological proteins (M-components) om 6,995 sera from an adult population. Acta Med Scand. 1966;179(2):235-47.

[14] Ruiz-Delgado GJ, Gómez Rangel JD. Monoclonal gammopathy of undetermined significance (MGUS) in Mexican mestizos: one institution's experience. Gac Med Mex. 2004;140(4):375-79.

[15] Landgren O, Gridley G, Turesson I, Caporaso NE, Goldin LR, Baris D, Fears TR, Hoover RN, Linet MS. Risk of monoclonal gammopathy of undetermined signifi-

cance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. Blood. 2006;107(3):904-06.

[16] Landgren O, Katzmann JA, Hsing AW, Pfeiffer RM, Kyle RA, Yeboah ED, Biritwum RB, Tettey Y, Adjei AA, Larson DR, Dispenzieri A, Melton LJ 3rd, Goldin LR, McMaster ML, Caporaso NE, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. Mayo Clin Proc. 2007;82(12): 1468-73.

[17] Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood. 2008;111(7):3388-94.

[18] Greenberg AJ, Vachon CM, Rajkumar SV. Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites. Leukemia. 2012;26(4):609-14.

[19] Wadhera RK, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. Mayo Clin Proc. 2010;85(10):933-42.

[20] Ogmundsdóttir HM, Haraldsdóttir V, M Jóhannesson G, Olafsdóttir G, Bjarnadóttir K, Sigvaldason H, Tulinius H. Monoclonal gammopathy in Iceland: a population-based registry and follow-up. Br J Haematol. 2002;118(1):166-73.

[21] Neriishi K, Nakashima E, Suzuki G. Monoclonal gammopathy of undetermined significance in atomic bomb survivors: incidence and transformation to multiple myeloma. Br J Haematol. 2003;121(3):405-10.

[22] Iwanaga M, Tagawa M, Tsukasaki K, Kamihira S, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance: study of 52,802 persons in Nagasaki City, Japan. Mayo Clin Proc. 2007;82(12):1474-79.

[23] Barría K, Maldonado J, Álvarez R, Rodríguez M, Cortés M. Case study of monoclonal gammopathy of undetermined significance and multiple myeloma at "Hospital Naval Almirante Nef" Viña del Mar, Chile. Rev Med Chil. 2010;138(6):788-90.

[24] Watanaboonyongcharoen P, Nakorn TN, Rojnuckarin P, Lawasut P, Intragumtornchai T. Prevalence of monoclonal gammopathy of undetermined significance in Thailand. Int J Hematol. 2012;95(2):176-81.

[25] Park HK, Lee KR, Kim YJ, Cho HI, Eun Kim J, Woong Kim K, Jung Kim Y, Lee KW, Hyun Kim J, Bang SM, Lee JS. Prevalence of monoclonal gammopathy of undetermined significance in an elderly urban Korean population. Am J Hematol. 2011;86(9): 752-55.

[26] Eisele L, Dürig J, Hüttmann A, Dührsen U, Assert R, Bokhof B, Erbel R, Mann K, Jöckel KH, Moebus S; Heinz Nixdorf Recall Study Investigative Group. Prevalence

and progression of monoclonal gammopathy of undetermined significance and light-chain MGUS in Germany. Ann Hematol. 2012;91(2):243-48.

[27]   Kyle RA, Therneau TM, Rajkumar SV, Remstein ED, Offord JR, Larson DR, Plevak MF, Melton LJ 3rd. Long-term follow-up of IgM monoclonal gammopathy of unde-termined significance. Blood. 2003;102(10):3759-64.

[28]   Bird J, Behrens J, Westin J, Turesson I, Drayson M, Beetham R, D'Sa S, Soutar R, Wa-age A, Gulbrandsen N, Gregersen H, Low E; Haemato-oncology Task Force of the British Committee for Standards in Haematology, UK Myeloma Forum and Nordic Myeloma Study Group. UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). Br J Haematol. 2009;147(1):22-42.

[29]   Rajkumar SV, Kyle RA, Therneau TM, Melton LJ 3rd, Bradwell AR, Clark RJ, Larson DR, Plevak MF, Dispenzieri A, Katzmann JA. Serum free light chain ratio is an inde-pendent risk factor for progression in monoclonal gammopathy of undetermined sig-nificance. Blood. 2005;106(3):812-17.

[30]   Rajkumar, S.V. MGUS and smoldering multiple myeloma: update on pathogenesis, natural history, and management. Hematology Am Soc Hematol Educ Program. 2005:340-5.

[31]   Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R, Palumbo A, Jagan-nath S, Blade J, Lonial S, Dimopoulos M, Comenzo R, Einsele H, Barlogie B, Ander-son K, Gertz M, Harousseau JL, Attal M, Tosi P, Sonneveld P, Boccadoro M, Morgan G, Richardson P, Sezer O, Mateos MV, Cavo M, Joshua D, Turesson I, Chen W, Shi-mizu K, Powles R, Rajkumar SV, Durie BG; International Myeloma Working Group. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia. 2009;23(2):215-24.

[32]   Kyle RA, Buadi F, Rajkumar SV. Management of monoclonal gammopathy of unde-termined significance (MGUS) and smoldering multiple myeloma (SMM). Oncology. 2011;25(7):578-86.

[33]   Dispenzieri A, Katzmann JA, Kyle RA, Larson DR, Melton LJ 3rd, Colby CL, Ther-neau TM, Clark R, Kumar SK, Bradwell A, Fonseca R, Jelinek DF, Rajkumar SV. Prev-alence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet. 2010;375(9727):1721-28.

[34]   Hutchison CA, Plant T, Drayson M, Cockwell P, Kountouri M, Basnayake K, Har-ding S, Bradwell AR, Mead G. Serum free light chain measurement aids the diagno-sis of myeloma in patients with severe renal failure. BMC Nephrol. 2008;9:11.

[35]   Tate J, Bazeley S, Sykes S, Mollee P. Quantitative serum free light chain assay - Ana-lytical issues. Clin Biochem Rev. 2009;30(3):131-40.

[36] Rajkumar SV, Kyle RA, Buadi FB. Advances in the diagnosis, classification, risk strat-ification, and management of monoclonal gammopathy of undetermined signifi-cance: implications for recategorizing disease entities in the presence of evolving scientific evidence. Mayo Clin Proc. 2010;85(10):945-48.

[37] Kyle R.A, Therneau, T.M, Rajkumar, S.V, Larson, D.R, Plevak, M.F, Melton, L.J, III. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. Mayo Clin Proc. 2004;79:59-66.

[38] Rawstron AC, Orfao A, Beksac M, Bezdickova L, Brooimans RA, Bumbea H, Dalva K, Fuhler G, Gratama J, Hose D, Kovarova L, Lioznov M, Mateo G, Morilla R, Mylin AK, Omedé P, Pellat-Deceunynck C, Perez Andres M, Petrucci M, Ruggeri M, Rym-kiewicz G, Schmitz A, Schreder M, Seynaeve C, Spacek M, de Tute RM, Van Valcken-borgh E, Weston-Bell N, Owen RG, San Miguel JF, Sonneveld P, Johnsen HE. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. Haematologica. 2008;93(3):431-38.

[39] Ocqueteau M, Orfao A, Almeida J, Bladé J, González M, García-Sanz R, López-Berges C, Moro MJ, Hernández J, Escribano L, Caballero D, Rozman M, San Miguel JF. Im-munophenotypic characterization of plasma cells from monoclonal gammopathy of undetermined significance patients. Implications for the differential diagnosis be-tween MGUS and multiple myeloma. Am J Pathol. 1998;152(6):1655-65.

[40] Pérez-Persona E, Vidriales MB, Mateo G, García-Sanz R, Mateos MV, de Coca AG, Galende J, Martín-Nuñez G, Alonso JM, de Las Heras N, Hernández JM, Martín A, López-Berges C, Orfao A, San Miguel JF. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple mye-loma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood. 2007;110(7):2586-92.

[41] Weiss BM, Kuehl WM. Advances in understanding monoclonal gammopathy of un-determined significance as a precursor of multiple myeloma. Expert Rev Hematol. 2010;3(2):165-74.

[42] Landgren O, Waxman AJ. Multiple myeloma precursor disease. JAMA. 2010;304(21): 2397-04.

[43] Anderson KC, Carrasco RD. Pathogenesis of myeloma. Annu Rev Pathol. 2011;6:249-74.

[44] Zingone A, Kuehl WM. Pathogenesis of monoclonal gammopathy of undetermined significance and progression to multiple myeloma. Semin Hematol. 2011;48(1):4-12.

[45] Rajkumar SV. Prevention of progression in monoclonal gammopathy of undeter-mined significance. Clin Cancer Res. 2009; 15(18):5606-08.

[46] Bergsagel PL, Kuehl WM. Chromosome translocations in multiple myeloma. Onco-gene. 2001;20(40):5611-22.

[47] Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. Blood. 2005;106(1):296-03.

[48] Fonseca R, Barlogie B, Bataille R, Bastard C, Bergsagel PL, Chesi M, Davies FE, Drach J, Greipp PR, Kirsch IR, Kuehl WM, Hernandez JM, Minvielle S, Pilarski LM, Shaughnessy JD Jr, Stewart AK, Avet-Loiseau H. Genetics and cytogenetics of multi-ple myeloma: a workshop report. Cancer Res. 2004; 64(4):1546-58.

[49] López-Corral L, Mateos MV, Corchete LA, Sarasquete ME, de la Rubia J, de Arriba F, Lahuerta JJ, García-Sanz R, San Miguel JF, Gutiérrez NC. Genomic analysis of high-risk smoldering multiple myeloma. Haematologica. 2012;97(9):1439-43.

[50] Chiecchio L, Dagrada GP, Ibrahim AH, Dachs Cabanas E, Protheroe RK, Stockley DM, Orchard KH, Cross NC, Harrison CJ, Ross FM; UK Myeloma Forum. Timing of acquisition of deletion 13 in plasma cell dyscrasias is dependent on genetic context. Haematologica. 2009;94(12):1708-13.

[51] Nishida K, Tamura A, Nakazawa N, Ueda Y, Abe T, Matsuda F, Kashima K, Taniwa-ki M. The Ig heavy chain gene is frequently involved in chromosomal translocations in multiple myeloma and plasma cell leukemia as detected by in situ hybridization. Blood. 1997;90(2):526-34.

[52] Avet-Loiseau H, Facon T, Daviet A, Godon C, Rapp MJ, Harousseau JL, Grosbois B, Bataille R. 14q32 translocations and monosomy 13 observed in monoclonal gammop-athy of undetermined significance delineate a multistep process for the oncogenesis of multiple myeloma. Intergroupe Francophone du Myélome. Cancer Res. 1999;59(18):4546-50.

[53] Fonseca R, Bailey RJ, Ahmann GJ, Rajkumar SV, Hoyer JD, Lust JA, Kyle RA, Gertz MA, Greipp PR, Dewald GW. Genomic abnormalities in monoclonal gammopathy of undetermined significance. Blood. 2002;100(4):1417-24.

[54] Malgeri U, Baldini L, Perfetti V, Fabris S, Vignarelli MC, Colombo G, Lotti V, Com-passo S, Bogni S, Lombardi L, Maiolo AT, Neri A. Detection of t(4;14)(p16.3;q32) chromosomal translocation in multiple myeloma by reverse transcription-polymer-ase chain reaction analysis of IGH-MMSET fusion transcripts. Cancer Res. 2000;60:4058-61.

[55] Ross FM, Chiecchio L, Dagrada G, Protheroe RK, Stockley DM, Harrison CJ, Cross NC, Szubert AJ, Drayson MT, Morgan GJ; UK Myeloma Forum. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in mon-oclonal gammopathies of undetermined significance. Haematologica. 2010;95(7): 1221-25.

[56] Zhan F, Barlogie B, Arzoumanian V, Huang Y, Williams DR, Hollmig K, Pineda-Ro-
man M, Tricot G, van Rhee F, Zangari M, Dhodapkar M, Shaughnessy JD Jr. Gene-
expression signature of benign monoclonal gammopathy evident in multiple
myeloma is linked to good prognosis. Blood. 2007;109(4):1692-00.

[57] Korde N, Kristinsson SY, Landgren O. Monoclonal gammopathy of undetermined
significance (MGUS) and smoldering multiple myeloma (SMM): novel biological in-
sights and development of early treatment strategies. Blood. 2011;117(21):5573-81

[58] Rasmussen T, Kuehl M, Lodahl M, Johnsen HE, Dahl IM. Possible roles for activating
RAS mutations in the MGUS to MM transition and in the intramedullary to extrame-
dullary transition in some plasma cell tumors. Blood. 2005;105(1):317-23.

[59] Chiecchio L, Dagrada GP, Protheroe RK, Stockley DM, Smith AG, Orchard KH,
Cross NC, Harrison CJ, Ross FM; UK Myeloma Forum. Loss of 1p and rearrange-
ment of MYC are associated with progression of smouldering myeloma to myeloma:
sequential analysis of a single case. Haematologica. 2009;94(7):1024-28.

[60] Wong KY, Huang X, Chim CS. DNA methylation of microRNA genes in multiple
myeloma. Carcinogenesis. 2012;33(9):1629-38.

[61] Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, Taccioli C, Zanesi N,
Alder H, Hagan JP, Munker R, Volinia S, Boccadoro M, Garzon R, Palumbo A, Aqei-
lan RI, Croce CM. MicroRNAs regulate critical genes associated with multiple myelo-
ma pathogenesis. Proc Natl Acad Sci U S A. 2008;105(35):12885-90.

[62] Jones CI, Zabolotskaya MV, King AJ, Stewart HJ, Horne GA, Chevassut TJ, Newbury
SF. Identification of circulating microRNAs as diagnostic biomarkers for use in mul-
tiple myeloma. Br J Cancer. 2012;107(12):1987-96.

[63] López-Corral L, Gutiérrez NC, Vidriales MB, Mateos MV, Rasillo A, García-Sanz R,
Paiva B, San Miguel JF. The progression from MGUS to smoldering myeloma and
eventually to multiple myeloma involves a clonal expansion of genetically abnormal
plasma cells. Clin Cancer Res. 2011;17(7):1692-00.

[64] López-Corral L, Sarasquete ME, Beà S, García-Sanz R, Mateos MV, Corchete LA,
Sayagués JM, García EM, Bladé J, Oriol A, Hernández-García MT, Giraldo P, Hernán-
dez J, González M, Hernández-Rivas JM, San Miguel JF, Gutiérrez NC. SNP-based
mapping arrays reveal high genomic complexity in monoclonal gammopathies, from
MGUS to myeloma status. Leukemia. 2012;26(12):2521-29.

[65] Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its pre-
malignant precursor. J Clin Invest. 2012;122(10):3456-63.

[66] Chesi M, Bergsagel PL. Many multiple myelomas: making more of the molecular
mayhem. Hematology Am Soc Hematol Educ Program. 2011;2011:344-53.

[67] Bianchi G, Kyle RA, Colby CL, Larson DR, Kumar S, Katzmann JA, Dispenzieri A,
Therneau TM, Cerhan JR, Melton LJ 3rd, Rajkumar SV. Impact of optimal follow-up

of monoclonal gammopathy of undetermined significance on early diagnosis and prevention of myeloma-related complications. Blood. 2010;116(12):2019-25.

[68] Bhattacharyya J, Mihara K, Takihara Y, Kimura A. Successful treatment of IgM-monoclonal gammopathy of undetermined significance associated with cryoglobulinemia and cold agglutinin disease with immunochemotherapy with rituximab, fludarabine, and cyclophosphamide. Ann Hematol. 2012;91(5):797-99.

[69] Pepe J, Petrucci MT, Mascia ML, Piemonte S, Fassino V, Romagnoli E, Minisola S. The effects of alendronate treatment in osteoporotic patients affected by monoclonal gammopathy of undetermined significance. Calcif Tissue Int. 2008;82(6):418-26.

[70] Berenson JR, Yellin O, Boccia RV, Flam M, Wong SF, Batuman O, Moezi MM, Woytowitz D, Duvivier H, Nassir Y, Swift RA. Zoledronic acid markedly improves bone mineral density for patients with monoclonal gammopathy of undetermined significance and bone loss. Clin Cancer Res. 2008;14(19):6289-95.

[71] Ballester OF. Omega 3 Supplementation for the Prevention of Disease Progression in Early Stage Chronic Lymphocytic Leukemia (ES-CLL), Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). US National Institutes of Health; 2009. http://clinicaltrials.gov (accessed December 5, 2012).

[72] Zonder JA, Karmanos BA. Green tea extract in treating patients with monoclonal gammopathy of undetermined significance and/or smoldering multiple myeloma. US National Institutes of Health; 2009. http://clinicaltrials.gov (accessed December 5, 2012).

[73] Golombick T, Diamond TH, Badmaev V, Manoharan A, Ramakrishna R. The potential role of curcumin in patients with monoclonal gammopathy of undefined significance - Its effect on paraproteinemia and the urinary N-telopeptide of type I collagen bone turnover marker. Clin Cancer Res. 2009;15(18):5917-22.

[74] Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. Am J Hematol. 2012;87(5):455-60.

[75] Bharti AC, Donato N, Singh S, Aggarwal BB. Curcumin (diferuloylmethane) downregulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Blood. 2003;101(3):1053-62.

[76] Bharti AC, Takada Y, Aggarwal BB. Curcumin (diferuloylmethane) inhibits receptor activator of NF-kappa B ligand-induced NF-kappa B activation in osteoclast precursors and suppresses osteoclastogenesis. J Immunol. 2004;172(10):5940-7.

[77] Vermorken AJ, Zhu J, Van de Ven WJ. Is curcumin for monoclonal gammopathy of undetermined significance without risk?-letter. Clin Cancer Res. 2010;16(7):2225.

[78] Rajkumar SV. Preventive strategies in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Am J Hematol. 2012;87(5):453-54.