# Monoclonal Gammopathy of Undeterminated Significance: Introduction and Current Clinical Issues

## Monoklonální gamapatie nejasného významu: Úvod a současné klinické problémy

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### Summary
Monoclonal gammopathy of undetermined significance (MGUS) is a precancerosis comprising two different kinds of cancer: lymphoid/lymphoplasmocytoid MGUS and plasma cell MGUS that represents about 85% of all MGUS cases. This type of MGUS has low but persistent tendency to transform to malignant disease, mainly multiple myeloma (MM), with frequency of about 1% per year. Using known risk stratification models based on clinical parameters, it is possible to identify patients' groups with average rates of progression as low as 0.26% and as high as 12% per year. However, due to the lack of clear genetic and/or phenotypic markers distinguishing MGUS from MM, we are not able to predict if and when MGUS will progress to MM in individual patients. There are partially overlapping molecular pathogenic events shared by MGUS and MM. Better understanding of pathogenesis of MGUS and MM using molecular-genetic approaches will help disclose the mechanisms of myeloma genesis; it can be also useful for identification of novel molecular targets. The ultimate goal for the near future is to develop better markers for definition of high-risk MGUS patients who will be candidates for early treatment intervention.

### Key words
monoclonal gammopathy of undeterminated significance – multiple myeloma – progression – molecular-genetic approach

### Souhrn
Monoklonální gamapatie nejasného významu (MGUS) je prekanceróza, která zahrnuje dva různé druhy: lymfatický/lymfoplazmatický MGUS a MGUS plazmatických buněk, který představuje zhruba 85 % všech případů MGUS. Tento typ MGUS má nízké, ale trvalé tendence k transformaci v maligní onemocnění, především mnohočetný myelom (MM), s frekvencí cca 1 % ročně. Pomocí známých modelů stratifikace rizika je možné určit na základě klinických parametrů skupiny pacientů, kteří progredují v rozmezí od 0,26 % do 12 % ročně. Avšak vzhledem k nedostatku jasných genetických a/nebo fenotypových znaků je rozlišení MGUS a MM těžké. Nejsme schopni předvídat, zda a kdy bude u jednotlivých pacientů MGUS progredovat do MM. Současně se částečně překrývají molekulární abnormality sdílené MGUS a MM. Lepší pochopení patogeneze MGUS a MM pomocí molekulárně-genetického přístupu pomůže odhalit mechanizmy vzniku myelomu, a to může být také užitečné pro identifikaci nových molekulárních cílů. Konečným cílem pro nejbližší budoucnost je vytvořit lepší ukazatele pro vymezení vysoce rizikových MGUS pacientů, kteří budou kandidáty na včasnou léčebnou intervenci.

### Klíčová slova
monoklonální gamapatie nejasného významu – mnohočetný myelom – progrese – molekulárně-genetická vyšetření

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## Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of monoclonal protein (M-protein), which can be detected in serum and/or urine and does not fulfill diagnostic criteria of multiple myeloma (MM), macroglobulinemia (WM), amyloidosis (AL) or other malignant lymphoproliferative diseases [1]. MGUS is characterized by presence of < 30 g/L of monoclonal protein (M-Ig), < 10% of bone marrow plasma cells infiltration and no organ damage [2,3]. MGUS is the most frequently occurring form of monoclonal gammopathies, accounting for 50% of all gammopathies [4]. The incidence of MGUS increases with age. For people younger than 50 years, the incidence of MGUS is less than 0.2%, over 70 years, it is about 3% [5]. MGUS incidence is varied in different ethnic groups, as confirmed by a study describing presence of M-protein in 8.6% of blacks compared to 3.6% in Caucasians and only 2.7% in Japanese [6].

Kyle in 1978 coined the name MGUS, which defined clinically asymptomatic state of benign plasmocytes proliferation and production of M-protein [7]. Although MGUS is a plasma cell disorder, there is a permanent risk of progression to malignant disease. The progression risk of MGUS to MM or other lymphoproliferative disease is 1% per year. During 25-year follow-up of MGUS patients at the Mayo clinic, the probability of progression was approximately 30% [8]. Time does not decrease the risk of progression, and this risk persists even in patients with long-term stable disease [4]. Lymphoplasmacytoid or lymphoid MGUS (10–15% of all MGUS) usually secrete IgM; if they progress, than into lymphoma or WM [9]. Plasma cell MGUS, compromising about 85% of all MGUS, expresses intact Ig or only Ig light chains when progression to MM or related plasma cells disorders occurs, it is characterized by clonal Ig of the same isotope [9,10].

The events that trigger progression of MGUS will be of prime interest. Recently, a key question whether MM is always preceded by MGUS, or if MM typically arises *de novo* has been answered (Fig. 1). According to several independent studies, most, if not all cases of MM, are preceded by MGUS [11–13]. It is expected that a premalignant plasma-cell proliferative stage characterized by asymptomatic M-protein production which is clinically defined as plasma MGUS is a preceding state in all MM patients. Based on this finding, it is important to identify reliable risk factors for MGUS progression to MM and to improve our knowledge of underlying mechanisms of transformation from MGUS to MM, with the aim to define better predictive markers for progression. MM is a well known incurable disease with many complications that reduce the quality of life and median survival of only 5–9 years [14]. Therefore, prevention of MGUS progression to MM is of primary importance.

## Definition of High-risk MGUS

Several clinical parameters are associated with increased rate of progression of MGUS to MM: size and type of M-protein and its free light and heavy chains, albumin, beta2microglobulin, bone marrow infiltration by clonal plasma cells, presence of circulating plasma cells in peripheral blood [13,15], microvascular density in bone marrow angiogenesis, cytokine network operation and immunoparesis [2], cytogenetic abnormalities, gene expression profiling and microRNA [16,17], aneuploidy detected by flow cytometric analysis of DNA content, abnormal plasma cells greater than 95% [15]. Based on multivariate analysis, it was possible to determine the prognosis of benign or low-risk MGUS and malignant or high-risk MGUS and identify patients' groups with average rates of progression as low as 0.26% and as high as 12% per year [2,13,18,15]. These currently available models of risk stratification demonstrate success in this field. However, drawbacks of this model are partial overlap and the fact that patients who progressed from MGUS to symptomatic MM required treatment in 72–76% after 5 years in high-risk group of MGUS which is still not fully clinically relevant. This indicates the need for development of better risk stratification criteria. New prognostic tools using old and new reliable markers should define ultra high-risk group MGUS patients with 90% probability of transition to symptomatic MM during three years of follow-up.

Hevylite chains measurement is a specific biochemic approach, which includes specific heavy and light chains, and points to suppression of isotype-specific immunoglobulin production. Thus, IgG HLC pair suppression was more frequent than suppression of Igs from other heavy chain classes, and MGUS patients who eventually progressed had a 2-fold higher rate of isotype specific suppression than stable MGUS patients [22–24]. The prognostic value of heavy light chain ratio (HLC) is compared to the international staging system (ISS). It seems that use of HLC ratio provides measure of immunoglobulin production and immunoparesis. It can form useful additions to current international staging system (ISS) assessment.

Clinical trials showed there is a possibility to delay or even prevent the development of active MM using a very safe and well tolerated treatment with lenalidomide how we can see in clinical trial Mateos et al [19]. But this argument is based on internal analysis of the data and can not demonstrate the unique benefits before the final conclusions of the study [19]. It is reasonable that these ultra high-risk patients will become candidates for early treatment intervention.

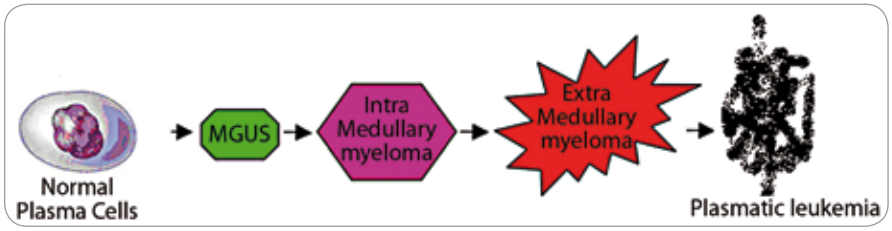


**Fig. 1. Multistep molecular process of PC transformation (modified by Hideshima 2004 and Pichorri 2008) [25, 26].**

## Scientific Problem or Opportunity in Definition of Clonal and Normal Plasmocytes

Molecular-genetic approaches used for better identification of MGUS signature profiles could improve the insight into MM precursor disease and may have a dramatic impact on clinical management in the future. But key biological and molecular-genetic mechanisms for MGUS development are not yet fully understood as it is a complicated process which involves many factors. However, the lack of unequivocal phenotypic, genetic and biochemical markers distinguishing MGUS from MM, makes it difficult to predict if and when MGUS will progress to MM.

Flow cytometry and genomic approaches (described in this issue of the Supplement) have been useful in identification of subtypes of MGUS and MM with important clinical implications for prognosis and subsequent treatment. As the number of clonal PCs is an independent predictive marker of progression, focusing on its appropriate determination is very important. Development of flow cytometry showed that basic analysis using only 2 markers (CD19 and CD56) for identification of CD38+CD138+ PC clonality is insufficient, especially in MGUS cases where mixture of clonal and polyclonal PCs can be found. Nowadays, 8-colour flow cytometry including intracellular light chains kappa/lambda expression, together with CD45 and CD27 analysis, should be used for verification of PC clonality on cellular level as not all CD19+ PC are normal and the whole population of CD19– and/or CD56+ PC may not be clonal. Based on our experience in the Laboratory of molecular cytogenetics, it seems that the description of phenotype of normal PCs is not perfect, since even this population of normal cells contains chromosome aberrations, e. g. polyclonal CD19+ PC are already abnormal with IgH disruption as marker of early oncogenetic event. Also, lower proportion of plasmocytes with genetic abnormalities in MGUS compared to MM could be due to low number of PCs, lower percentage of clonal PCs and coexistence of normal and clonal PCs in MGUS bone marrow [20,21]. It is obvious that current phenotypical definition of normal PCs is challenging by research findings on genomic level. Molecular-genetic approaches used for better identification of MGUS signature profiles could improve the insight into MM precursor disease and may have a dramatic impact on clinical management in the future. But key biological and molecular-genetic mechanisms for MGUS development are not yet fully understood as it is a complicated process which involves many factors. Genetic aberrations detected in MGUS have been also found in MM making it hard to distinguish these two clinical entities [27]. GEP (gene expression profiling) is a novel genomic method that would greatly improve current knowledge about changes in gene expression in MGUS in comparison to MM. The major obstacle of general usage of this method is the low number of cells obtained from MGUS patients and minimal yield of RNA from these samples. New ways of isolation are desperately needed and are discussed in another part of this supplementum.

## Conclusion

Prevention of MGUS progression to MM is of primary importance, since MM is a well-known incurable disease with many complications that reduce the quality of life. There are some questions that need to be answered. Are there phenotypic or genetic markers that can distinguish MGUS and MM from each other? Is the progression from MGUS to MM mediated by acquisition of somatic genetic abnormalities in the tumor cells and/or by non-tumor cell changes? Is it possible to develop better stratification models to predict the probability that any given MGUS will progress to MM?

Can we identify effective treatment protocols that will eliminate malignant cells or significantly prevent progression to MM? We consider it important to identify those patients who may benefit from early treatment and to allow development of intervention strategies based on rational science and understanding of disease biology.

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