

**Review Articles****Non-Secretory Myeloma: Ready for a new Definition?**

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Abstract. Non-secretory myeloma is a rare myeloma subtype whose diagnosis, until a few years ago, was established by demonstration of monoclonal plasma cells $\geq 10\%$ in the bone marrow and by negative results on serum and urine electrophoresis and immunofixation studies. However, this type of myeloma could be misdiagnosed if the workup does not include an accurate study of serum free light chain test since some of the patients diagnosed as non-secretory could be light chain only with small amounts monoclonal proteinuria. Due to this limit in classification, all the information available today, generally coming from retrospective studies including patients studied completely and incompletely, could be misleading. A new definition is, thus, needed to distinguish between the true non-secretory, with a possible better prognosis, and the other forms of oligo-secretory myeloma with a prognosis more similar to the secretory form of myeloma. With all the data of the literature, the availability of laboratory and radiological tools, times are mature to depict a new definition of nonsecretory myeloma that deserves a peculiar work up and different response evaluation and, may be, a different therapeutic approach.

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Introduction. Multiple myeloma (MM) is a malignancy of plasma cells defined by infiltration of bone marrow, and presence of CRAB feature (skeletal lesions, anemia, bone pain, renal insufficiency, hypercalcemia) as well as 3 specific biomarkers: clonal bone marrow plasma cells $\geq 60\%$, serum free light chain (FLC) ratio ≥ 100 (provided involved FLC level is ≥ 100 mg/L), and more than one focal lesion on magnetic resonance imaging (MRI).^{1,2} In the USA this hematologic malignancy accounts for approximately 10% of all hematologic neoplasm and 1% of all malignant disease, being twice as common in African-Americans compared with Caucasians and lowest among the Chinese and Japanese.^{1,2} In Italy data are similar, MM accounting of 1% of all cancers

and 13% of all hematologic malignancies.³ MM cells represent the neoplastic counterpart of normal plasma cells, and thus the hallmark of most neoplastic plasma cells is the persistent production of clonal immunoglobulin, albeit completely non-functional, either complete (heavy and light chain) or as part of immunoglobulins (heavy chain or light chain). The availability of this protein in the blood or urine for quantitative assessment using serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), or the serum free light chain assay allows easy monitoring of response in most cases of myeloma.^{4,5}

Monoclonal component (MC) typically can be detected in serum and/or urine as:

1) high concentrations of a full Ig molecule consisting of heavy and light chains bound together;

2) elevated levels of the complete Ig molecule plus high concentrations of light chains unbound to heavy chain (free light chains [FLCs]);

3) primarily FLC in the presence of minimal amounts or even no complete Immunoglobulin (Ig) whatsoever which is rare;

4) a fourth entity, characterized by the absence of detectable MC either in the serum or the urine, represents a very small subset of the myeloma population.

The incidence of these non-secretory multiple myelomas (NSMMs) ranges from 3% to 5% of the total MM population.⁶⁻⁸ However, advances in the detection of serum FLCs have demonstrated that most of these previously defined NSMMs are probably oligo secretors,⁹ namely producing primarily or solely serum FLC in the absence of heavy chain. Thus, the proportion of true NSMM, meaning MM that secretes no measurable monoclonal heavy or light chains at all, is closer to 1–2% of all MMs.^{1,10}

Non-secretory myeloma is classically defined as clonal bone marrow plasma cells $\geq 10\%$ or biopsy proven plasmacytoma, evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically hypercalcemia, renal insufficiency, anemia, or bone lesions, and lack of serum and urinary monoclonal protein on electrophoresis and immunofixation.⁸⁻⁹ Clinically, patients who present with true non-secretory disease at diagnosis behave differently from patients who present with the oligo-secretory disease, as well as from those who progress from having secretory disease at diagnosis to oligo-secretory or non-secretory disease at the time of relapse.

In this article, we review all the information available on this particular entity trying to outline a possible definition of different subsets of non-secretory myeloma.

Biological Basis. Non-secretory myeloma patients can be divided into several groups. The true non-secretory myeloma should be considered only the group of non-producers patients, whose tumors have a defect in immunoglobulin synthesis, resulting in no measurable protein in the blood or urine, although they still have a significant plasma cell burden in the bone marrow and evidence of

end-organ damage.¹¹ In these patients, even the use of the FLC assay will not reveal measurable disease as currently defined.¹² The next category of non-secretory myeloma patients consists of those cases whose neoplastic plasma cells produce an altered MC but have defects in secretion. The exact mechanisms that prevent either production or secretion of monoclonal Ig by NSMM remain poorly understood. One hypothesis argues that true NSMMs arise from a consecutive loss of secretion, firstly of heavy chains and then light chains.¹³ It has been demonstrated in vitro that a single amino acid substitution in a light chain can potentially block secretion outside the cell and that a mutation in the immunoglobulin gene can account for the lack of secretion in a patient with non-secretory myeloma.¹⁴ On the other hand, patients presenting only immunoglobulin light chains in serum and urine, and then affected by light chain MM, never displayed a functional IgH recombination.¹⁵ The absence of legitimate IgH rearrangement at the DNA level, reflecting possible abnormalities in the IgH gene recombinations during B-cell maturation, permits the secretion in the abnormal plasma cells of the only light chains.¹⁵ One study in 2002 found that 11 out of 14 NSMM patients had a t(11;14)(q13;q32) rearrangement, which the authors postulated gave the cells a more “lymphoplasmacytic morphology” with a lower secreting capacity than MM cells without the translocation.¹⁶ Interestingly, the same translocation was detected in the MM case report detailed earlier that also demonstrated the frameshift mutation in the gene coding the light-chain constant region, functionally preventing secretion of the kappa light chain.¹⁴ These data, taken together, suggest that the “evolution” of NSMM cells may be stepwise from fully secretory MM to MM that loses production of the heavy chain and then in a subsequent step fails production of the light chain.

Among patients whose tumors have defects in Ig production, there is a subset of patients who have impaired secretion but can produce a small amount of light chains. These are patients who met criteria for oligo-secretory “free light only” myeloma, since their protein secretion may not be as high as that seen in typical myeloma, but it can be measured using current technology, in particular, serum FLC assay.¹⁷ Oligo-secretory multiple myeloma is often characterized by serum protein of < 1.0 g/dL, urine protein of < 200 mg/24

hrs, and free light chain values of < 100 mg/L (or 10 mg/dL).¹¹ Clinically, patients who present with true non-secretory disease at diagnosis behave differently from patients who present with oligo-secretory disease at the onset, as well as from those who progress from having secretory disease at diagnosis to oligo-secretory or non-secretory disease at the time of relapse (free light chain “escape”). These latter patients typically have high-risk myeloma, genomic instability, and rapid clonal evolution.¹⁸⁻¹⁹

The International Myeloma Working Group still defines NSMM as MM lacking monoclonal protein by serum or urine immunofixation, which can include light-chain MM with quite high levels of monoclonal FLCs detected solely by the sFLC assay.^{11,17} However, this definition is probably not sufficient, since the MM indeed is actively secreting a component of Ig. Thus, cases of NSMM can more accurately be subclassified into at least four distinct categories with separate molecular mechanisms:

1) Oligo-secretors/FLC-restricted MMs: as discussed most of these cases can be followed by sFLC assay.¹⁷

2) Non-producers: MM is non-secretory due to a complete, real absence of any Ig production whatsoever. Such rare patients would not be able to be monitored by either traditional methods or intracellular immunofluorescence, which can be used to detect monoclonal Ig in the cytoplasm of many cases of NSMM. It is hypothesized that the mechanism of non-production is the loss of sFLC secretion by MM clones, which were initially FLC secretors, although this has not been definitively proven.

3) True non-secretors: these MM cells produce Ig molecules but are unable to secrete them (the variety of mechanisms by which this occurs is discussed in detail in the following)

4) False non-secretors: MM variants or related plasma cell diseases that had measurable intracellular Ig by immunofluorescence but no measurable extracellular component by conventional testing. A straight pathological evidence that they are secreted (such as Ig deposits found in renal biopsies) can be accessed as part of the recently described entity monoclonal gammopathy of renal significance).^{12,20-21} Furthermore, some data are suggesting that these Igs are secreted in vesicles via budding off of the cell membrane, rendering them undetectable in the

serum. This would represent a challenge for detection and treatment, too.

Workup and Prognosis. The standard workup for any patients with known or suspected non-secretory myeloma as recommended by the 2003 consensus statement from the International Myeloma Workshop¹¹ includes SPEP, UPEP, and serum free light chain assay, in addition to imaging survey (**Table 1**). All patients with suspected MM, including NSMM, should undergo bone marrow aspiration (or biopsy of suspected plasmacytomas) completed by flow cytometry and CD138-enriched fluorescent in situ hybridization testing. If true NSMM is suspected, samples should also be stained for intracellular Ig. As in all other forms of symptomatic MM, NSMM requires the presence of any myeloma-defining events and/or evidence of MM-mediated end-organ damage such as hypercalcemia, anemia, or bone lesions to differentiate an asymptomatic MM precursor from actual MM.²

Patients with light chain myeloma may have only a serum free light chain abnormality, although these patients should not be considered to have right non-secretory myeloma. The group of true NSMM does not show measurable disease with no serum/urine monoclonal component, or free light chain assay abnormalities. In these patients, who are typically characterized by the absence of any easily measurable parameter, a skeletal survey is performed with a novel more sensitive and functional methods. In particular positron emission tomography (PET)/CT scan bone survey, along with marrow plasmacytosis, can serve as a relatively objective assay to assess the extension of disease at presentation and the level of disease response. PET/CT imaging can help identify sites of bone disease and to distinguish between active and quiescent lesions at treatment completion and during follow-up.²²

Table 1. Recommended work-up of suspected non secretory myeloma.

Routine chemistry, including LDH and beta2microglobulin
CBC with differential
SPEP with immunofixation
Quantitative immunoglobulins (including IgD or IgE if suspected)
24-hr urine test with protein quantification and immunofixation
Serum free light chain assay
PET/CT scan

Given the rarity of NSMM in the overall MM population, its clinical course and prognosis are still not thoroughly characterized. Moreover, since monitoring of the Ig is essential to evaluate response to therapy and to detect relapse, NSMM patients are usually excluded from clinical trials. Results on the characteristics and the outcome of NSMM are not univocal. In a series from France, it was reported that there was a higher proportion of patients with the t(11;14) translocation among patients with non-secretory myeloma.¹⁶ The frequency of this translocation in non-secretory myeloma patients was 83% in a cohort of 24 patients. In a group of 127 myeloma patients from the UK who had undergone transplantation, 6 were found to be patients with the non-secretory disease. The overall survival (OS) and progression-free survival (PFS) of this small group of patients were found to be superior to those of the patients with a traditional secretory myeloma phenotype (36 vs 23 months).²³ A possible hypothesis for this could be that there is a lower frequency of high-risk genetic alterations in the non-secretory patients, which allows their improved outcomes respect to patients with IgG, IgA, or light chain myelomas.¹⁶ In 1986, Smith et al. released a case series that included 13 NSMM patients, in which NSMM patients had a median survival of 46 months compared to 22 months for secretors. At that time, ELISA-based SFLC testing was not commercially available, and therefore it is unclear how many of the NSMM patients had light-chain oligo-secretory MMs.²⁴

By contrast, Kyle et al., in their 1,027 patients cohort, report an outcome for patients with non-secretory myeloma similar to that of patients with secretory myeloma (OS 38 vs 33.4 months).²⁵ Similarly, no difference in PFS or OS was observed in a series from the Center for

International Blood & Marrow Transplant Research (CIBMTR), among 110 patients with non-secretory myeloma compared with matched controls in a 4:1 fashion.²⁶ However, the number of true non-secretors vs those with the oligo-secretory disease was not available. Finally, Chawla et al. retrospectively examined the survival and prognosis of a group of NSMM patients. The study included 124 patients with non-secretory myeloma treated in a period from 1973 until 2012. Around two third of patients (88 pts) have been addressed before 2001 with conventional therapy (mainly chemotherapy) and one-third (36 pts) after 2001 when novel agents entered in routine clinical practice. The median follow-up was 102 months; the median PFS after initial therapy was 28.6 months and overall survival 49.3 months. They observed a significant improvement after 2001 (99 vs. 43 months), as also reported in general for myeloma. However, while survival before 2001 was similar in non-secretory and secretory patients (3.6 vs. 3.5 yrs), interestingly after 2001 non-secretory myeloma showed a significantly higher overall survival respect to secretory ones (8.3 vs. 5.4 yrs, p=0.03). Several factors were evaluated on survival, in multivariate analysis only age and the time-period of diagnosis were significantly correlated with a better outcome.²⁷ Since FLC assay was available only for 29 out of 124 entering the analysis, despite this study was performed on a very large group of patients, the percentage of patients who could be better defined as oligo-secretory MM was not determinable.

Actually, with all data available from the literature, there is no evidence for poor prognosis associated with NSMM phenotype (**CFR Table 2**).

Table 2. Summary of data on outcome of non-secretory myeloma coming from selected retrospective studies.

	N of patients	Median OS	Additional information
Terpos et al. ²³	127 (5% non-secretory MM)	79.7 months	Better PFS after transplant for non secretory myeloma (36.1 vs 23 months).
Smith et al. ²⁴	172 (7% non-secretory MM)	46 months	Better OS in non-secretory myeloma (median OS 46 months versus 21 months; p<0.01) Better OS in non-secretors with minimal lytic bone lesions (74 vs 21 months for patients with extensive bone disease).
Kyle et al. ²⁵	1027 (3% non-secretory MM)	38 months	OS similar to secretory myeloma (median OS 38 vs 33 months)
Kumar et al. ²⁶	110 (100% non-secretory)	69 months	Better PFS after transplant for non secretory myeloma (30 months vs 23 months, p=0.05) (
Chawla et al. ²⁷	124 (100% non-secretory)	49.3 months	OS was superior in non-secretory myeloma treated after 2001 (median OS 8.3 versus 5.4 years, P=0.03)

Treatment and Response Assessment. Although non-secretory myeloma usually is not included in protocols since the difficulty in monitoring the response, the few data available seems not to suggest that NSMM responds differently to standard MM treatments. Thus a standard approach including when possible autologous stem cell transplantation (ASCT) may do equally well if not better than secretory MM.^{23,27}

In a study on patients receiving lenalidomide, bortezomib, and dexamethasone (RVD) induction followed by early or late transplant, Nooka et al., reported a similar 3-year OS of > 85%, in all analyzed patients, secretory and non-secretory.²⁸ Terpos et al. as well, in a larger series of patients provided similar results, suggesting that the gains in outcomes associated with the use of new agents were similar for secretory and non-secretory myeloma patients.²³ Thus, until new evidence suggests other pathways, treatment of NSMM should follow the same guidelines as those provided for secretory MM.

Monitoring response of NSMM is a challenging. Serial bone marrow studies could be the gold standard, but the cost, time, and patient discomfort associated with frequent bone marrow aspirations and/or biopsies make them less feasible in real life. Also, routine marrow histology and routine flow cytometry are notoriously inaccurate, due in large part to the patchy nature of marrow involvement, which entails that the extent of marrow involvement at different sites can be heterogeneous within a single patient.²⁹ A possible solution can come from the use of multiparametric flow cytometry (MPF), which allows evaluating the marrow better. Moreover, the minimal residual disease (MRD), measured with MPF, has not only predictive but also prognostic implications in the setting of disease assessment post-transplant.³⁰ However, although the significant improvement of this technique over conventional flow cytometry or histologic assessment of plasma cell number, MPF need a partner to assess total body myeloma burden better. Therefore, the pairing of imaging and more sensitive marrow assessment represents an optimal procedure to evaluate response to therapy and MRD in non-secretory patients in whom the inability to use SPEP/UPEP/FLC tests limits response assessment. Since no data are available directly on non-secretory myeloma, information is extrapolated from a study on secretory MM, where magnetic resonance imaging

(MRI) and positron emission tomography (PET) are most adopted. In a systematic review, Regelin et al. observed, using X-rays as the gold standard, that both MRI and PET had a sensitivity of 90% (i.e. MRI and PET individually detected abnormalities in 90% of patients who had abnormal findings on X-ray). Furthermore, both methods identified a higher total number of lesions than X-rays, suggesting that both techniques were more sensitive than the standard.³¹ Several studies have demonstrated the diagnostic and prognostic role of PET and that a lack of a post-transplant normalization of standard uptake value activity strongly predicts a short duration of responses.³²⁻³⁵ On the other hand, of patients showing focal marrow lesions on MRI, only 33.5% of them achieving a very good partial response or better response by standard response criteria³⁶ had shrinkage of these lesions, suggesting inadequate sensitivity for detecting the response.³⁷⁻³⁸ Hence, MRI, although very sensitive for detecting lesions at diagnosis, is insufficient for monitoring, due to the practical limitations and the relatively static nature of bone despite tumor killing.

Thus, in the clinical practice, in NSMM patients with detectable lesions at diagnosis on PET/CT, this will be performed at intervals decided based on the duration of treatment cycles and the clinical circumstances. An aggressive disease and/or lack of other reliable clinical indicators of response suggest a more frequent checking with PET/CT, whereas an indolent disease and/or the presence of other clinical indicators, such as improvement in symptoms or cell counts permit a less frequent one. Even for patients in remission and undergoing long-term monitoring, the timing of PET/CT will be established in relation to the depth of response obtained and to the characteristics of patients before treatment. In these sets of patients, it is convenient to associate also a bone marrow evaluation with biopsies or MPF when available. In patients that cannot be followed by PET/CT, monitoring of disease will be based only on serial bone marrow aspirations and biopsies with the same criteria reported above (**Table 3**), associated to Rx.

Conclusions. Given the availability of higher sensitive methods for monoclonal component identification and quantification, particularly with the introduction of serum free light chain assay,

Table 3. Recommended tests to assess response and disease status in a patient with non-secretory myeloma.

Assess for improvement in baseline CRAB criteria that initiated treatment
Bone marrow aspirate and biopsy (consider the use of MPF to more accurately quantify plasma cell clone)
PET/CT scan

the subset of patients meeting criteria for true non-secretory MM has become more rare, with an estimated incidence closer to 1-2% of all MM diagnosis.

In the absence of any laboratory test easily measurable during therapy and follow-up, new cross sectional imaging modalities, in particular, PET-CT represents a useful tool in clinical practice for disease monitoring, at least in those fraction of patients with detectable lesions at the onset. In the absence of radiologically detectable lesions, serial bone marrow examinations for quantification of neoplastic plasma cell infiltration remains the only way for disease monitoring.

Due to the small proportion of patients encountering criteria for NSMM and the

systematic exclusion of these patients from the clinical trials, it is not possible to define if the prognosis of these patients is significantly different from secretory ones. Limited data available from the literature seem to show that the presence of a not secretory phenotype at the onset gives no additional risk for the outcome, unlike from what happens when an oligo or no secretory phenotype is acquired at relapse with the previously described phenomenon of free light chain escape. In the absence of more extensive data, NSMM deserves similar treatment of secretory MM. More studies ad hoc are needed to define the course and the outcome of this entity better.

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