

Reporting of monoclonal gammopathy testing in Switzerland: Recommendations of the Swiss Society for Allergology and Immunology (SSAI) - Commission Medical Laboratory Immunology (CMLI) and the Swiss Society of Clinical Chemistry (SSCC)

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Introduction

A diagnosis of monoclonal gammopathy often requires long-term patient monitoring and typically involves various medical specialists, including general practitioners and hematologists. Consequently, follow-up tests are commonly conducted in different medical laboratories, demanding a certain uniformity and comparability in the reporting of monoclonal gammopathies by diagnostic laboratories.

To evaluate the extent of variation in the reporting of monoclonal gammopathy laboratory testing in Switzerland, the Commission Medical Laboratory Immunology (CMLI) of the Swiss Society of Allergology and Immunology (SSAI) initiated a survey. This survey was sent to 44 different laboratories known to participate in national quality assurance schemes for the analysis of monoclonal gammopathies. The centers were asked to report the laboratory test results of five distinct gammopathy cases using their own routine reporting forms. Sixteen laboratories responded and the results revealed significant variations in reporting practices among the different centers.

Considering the critical need to reduce this reporting variation, recommendations were defined by the CMLI to harmonize reporting of monoclonal gammopathies testing by medical laboratories in Switzerland.

Terminology

The survey found that multiple terms are used in Switzerland to report monoclonal proteins, including paraprotein, monoclonal component, monoclonal protein, Bence-Jones protein, M-gradient, M-peak, and M-protein. While these terms are commonly used in scientific literature and everyday conversations, they usually originate from historical or technological contexts and may not reflect the importance of having a unified, formally accepted nomenclature.

To enhance clarity of reporting and reduce potential confusion among physicians, various groups, including the Australian Association of Clinical Biochemists [1], the Canadian Society of Clinical Chemists [2], and the College of American Pathologists in collaboration with the American Association for Clinical Chemistry and the American Society for Clinical Pathology [3] have recommended adopting a common terminology. However, there are differing opinions on the preferred nomenclature and a consensus between these different efforts has not been achieved. It is important to note that the consensus guidelines issued by the International Myeloma Working Group (IMWG), which are used by

the myeloma community globally, consistently use the term 'monoclonal protein', abbreviated as 'M-protein' [4].

In the light of the fact that the current laboratory recommendations lack a unified nomenclature, and the IMWG consistently uses the term 'monoclonal protein' to describe a monoclonal immunoglobulin, monoclonal free light chains, and monoclonal free heavy chains [4, 5], the CMLI recommends:

Recommendation 1:

When referring to a monoclonal immunoglobulin, monoclonal free light chain, or monoclonal free heavy chain in serum or urine, the term 'monoclonal protein', abbreviated to 'M-protein', (monoklonales Protein (M-Protein), protéine monoclonale (protéine-M), proteina monoclonale (M-proteina)), should be used. Other terminology should not be used. When referring to a specifically detected M-protein, its description should be added (e.g., M-protein IgG kappa, M-protein free kappa light chains, etc.).

Monoclonal protein characteristics

The survey revealed considerable variability in how information regarding the presence, isotype, and concentration of monoclonal proteins is reported. This variability includes not only whether these characteristics are included but also their placement within the report—either in distinct fields or as part of an interpretative comment.

Given that the identification of a monoclonal protein may indicate a serious disorder but must be considered alongside its concentration and isotype [4], and that these characteristics are critical for accurate diagnosis, risk stratification, treatment evaluation, and disease monitoring [5], the CMLI recommends the following:

Recommendation 2:

When reporting a monoclonal protein, both its isotype and concentration must be specified. To allow for clear and unambiguous interpretation as well as trending of results over time, distinct reporting fields should be used for these characteristics.

Monoclonal protein concentration

Most of the laboratories participating in the survey report the concentration of a detected M-protein as an absolute value (i.e. g/L). However, some laboratories also report the relative concentration of M-proteins as a percentage of the total protein concentration.

Considering that reporting both absolute and relative concentrations could lead to confusion or misinterpretation of the results, and that the clinical utility of relative concentrations is limited and does not correspond to the units specified in the IMWG consensus criteria for diagnosing of multiple myeloma and assessing response to treatment [4, 5], it is recommended that:

Recommendation 3:

The concentration of an M-protein should be reported solely in absolute values. Relative concentrations (i.e., percentages) should not be included. The units of measurement should be g/L for serum and mg/L for urine, or mg/24 h for 24-hour urine specimens.

Quantification of monoclonal proteins

When determining the concentration of an M-protein, quantitation can be complicated by the co-migration of other proteins in the electrophoresis beta- or gamma fraction. Two methods for the quantification of M-proteins are currently used: the perpendicular drop method and the tangent skimming method. Both methods have, however, limitations when it comes to accurately determining the M-protein concentration, and neither method is defined as the gold standard. Surveys and recommendations from other countries indicate a preference for the perpendicular drop method [6, 7], with one national recommendation suggesting it as the only acceptable method [8]. Regardless of the method used, it has been shown that there is greater imprecision and loss of accuracy at lower M-protein concentrations. Our survey however showed that only few laboratories mentioned that their quantification of M-proteins is inaccurate and imprecise in case of M-proteins co-migrating with beta-fraction proteins. To ensure proper interpretation of results, it is crucial to provide additional information where measurement precision is low [9].

Recommendation 4:

The quantification of an M-protein should be performed using the most accurate and precise method according to the laboratory's established standards. If the M-protein cannot be quantified with adequate accuracy and precision -such as in cases of beta-migrating M-proteins or low-concentration M-proteins- appropriate comments should be added to indicate the limitations.

Total immunoglobulin concentrations

Laboratory requests for monoclonal gammopathy testing often include the measurement of total immunoglobulin (Ig) concentrations. Our survey revealed that nearly all laboratories report total Ig concentrations regardless of the presence of an M-protein of the same isotype. However, two laboratories suppress the total Ig concentration in their reports by a comment when an M-protein of the same isotype is detected; one of these laboratories mentioned the concentration within the comment. Determining the M-protein concentration by total Ig measurements may be unreliable due to the presence of polyclonal Ig of the same isotype. Furthermore, methods used for total Ig concentrations, such as nephelometry and turbidimetry, may under- or overestimate an M-protein of the same isotype [10]. Some studies also highlight the risk of misinterpretation when reporting two separate results for the same Ig (e.g., total IgG concentration and M-Protein IgG kappa concentration) and recommend adding explanatory comments to clarify this [3, 6].

Recommendation 5:

The report should clearly and unequivocally identify the result representing the concentration of the M-protein. Any additional information that could be misinterpreted as the M-protein concentration should be omitted to prevent confusion.

Free light chains

Most laboratories participating in the survey do not indicate the assay used for quantifying free light chains (FLC) in serum, either in the report or elsewhere (e.g., the laboratory test catalogue). The IMWG diagnostic and response assessment criteria include FLC values measured using the Freelite® assay (Binding Site, Birmingham, UK) [4, 5]. Several FLC assays from different manufacturers are currently commercially available, and according to our survey, are also used by laboratories for routine diagnostics. As there is no international certified reference material available, these tests are not standardized and demonstrate significant inter-assay variation in both absolute concentrations and ratios [11-14]. Therefore, FLC values obtained from different assays are not interchangeable. Patient monitoring should thus be performed using the same assay to allow reliable evaluation of treatment response. In addition, using FLC values generated with assays other than Freelite® for the IMWG diagnostic and response criteria may be inappropriate.

Laboratories need to draw the attention of health care professionals to these issues to prevent confusion and misinterpretation at diagnosis or during patient follow up.

Recommendation 6:

Laboratories should disclose the assay used for free light chain quantification, preferably within the report or, alternatively, in a referred resource (e.g., the laboratory test catalogue). A comment should state that the reported free light chain results are not directly comparable with those of other assays, and that consistent use of the same assay is essential for patient follow-up.

Monoclonal free light chains

The laboratory detection of monoclonal free light chains in the absence of corresponding gamma, alpha, or mu heavy chain reactivity may indicate the presence of either monoclonal free light chains or a monoclonal IgD or IgE protein. The survey indicated that some laboratories do not have the possibility to detect monoclonal IgD or IgE proteins as part of their testing repertoire. In addition, some centers also do not routinely send samples to another laboratory for such IgE and IgD testing.

Although the prevalence of IgD and IgE myeloma is low, these diseases are often considered to have worse prognosis and more aggressive clinical features as compared to other isotypes [15]. The IgD and IgE M-protein levels may be low or even be undetectable by electrophoresis. Inappropriate laboratory testing may result in a delayed diagnosis which may contribute to poor survival rates in these patients. Correct identification of the M-protein isotype is critical for adequate diagnosis and monitoring of IgD and IgE plasma cell neoplasms.

Recommendation 7:

If a monoclonal light chain is detected in the absence of a corresponding monoclonal gamma, alpha, or mu heavy chain, laboratories should report the presence of a monoclonal free light chain only after having confirmed the absence of a corresponding monoclonal delta or epsilon heavy chain. Reporting monoclonal proteins without such complete isotype characterization should be avoided.

Therapeutic monoclonal antibodies

Most, but not all laboratories participating in the survey consider a patient's history of previous analyses when interpreting test results and comment on changes in migration profile or isotype of the detected monoclonal protein(s) during follow-up. Only a few laboratories comment on the potential presence of a therapeutic monoclonal antibody in cases involving a low-concentration M-protein.

A low-concentration (less than 2 g/L) M-protein may reflect an endogenous protein, but it could also represent a therapeutic monoclonal antibody. Reporting of an M-protein without a specific comment indicating this possibility may lead to a misdiagnosis of a monoclonal gammopathy. Furthermore, during the follow up of patients with multiple myeloma, a low-concentration M-protein may indicate residual disease but can also appear after hematopoietic stem cell transplantation in the context of immune system reconstitution. It is therefore crucial to report any observed change in migration profile or isotype and explicitly comment on the presence or absence of the original myeloma-associated M-protein. Failing to comment on M-proteins in these cases can lead to confusion and may be misinterpreted as disease persistence or relapse [5].

Therapeutic monoclonal antibodies, such as Daratumumab and Elotuzumab, are frequently part of the treatment regimen for myeloma patients, while Rituximab is widely used to treat patients with Waldenström macroglobulinemia [16, 17]. In addition, a vastly growing number of other therapeutic monoclonal antibodies are nowadays being used to treat a wide range of diseases not associated with monoclonal gammopathy. Typically, these therapeutics are of the IgG kappa isotype, although IgG lambda also exists. Other isotypes are in development.

The interference of a therapeutic monoclonal antibody with laboratory testing depends on the serum concentration, which in turn is affected by the administered dose and the time of blood sampling. Usually, the concentration of the therapeutic at the time of testing is low (i.e., below 2 g/l) [18, 19].

Laboratories encounter analytical and interpretative problems, particularly if the patient's M-protein and the therapeutic monoclonal antibody are of the same isotype and have similar electrophoretic mobility profiles. During treatment, the concentration of the patient's M-protein protein may fall below 2 g/L, causing difficulties to distinguish from the co-migrating therapeutic [19]. For evaluating response criteria or detecting a relapse, the discrimination of endogenous and therapeutic monoclonal proteins is crucial. It should be noted here that methods are commercially available to specifically identify and -thus- discriminate Daratumumab.

Recommendation 8:

When interpreting test results, the patients' previous results should be reviewed, and any changes in the monoclonal protein migration profile or isotype should be mentioned in the report. If a detected monoclonal protein shows characteristics indicative of a therapeutic monoclonal antibody (e.g., IgG isotype, low concentration below 2 g/l), laboratories should include a comment noting the possible presence of such a therapeutic agent.

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