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SPECIAL ARTICLE

Laboratory guidelines for the diagnosis and follow-up of patients with monoclonal gammopathies☆

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Monoclonal component

Abstract We present guidelines from the Immunochemistry group of the Spanish Society for Immunology that are designed to provide a practical tool for the diagnosis and follow-up of monoclonal gammopathies. We review the clinical and analytical features of various monoclonal gammopathies, international consensus guidelines and techniques used to detect and follow-up monoclonal components.

PALABRAS CLAVE
Mieloma;
Gammapatía monoclonal;
Inmunofijación;
Cadenas ligeras;

Guía de laboratorio para el diagnóstico y seguimiento de pacientes con gammapatías monoclonales

Resumen Se presenta una guía elaborada por el grupo de Inmunoquímica de la Sociedad Española de Inmunología con el objetivo de proporcionar una herramienta práctica para el diagnóstico y seguimiento de las gammapatías monoclonales.

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◊ There is more information on the members of the Immunochemistry Group of the Spanish Society of Immunology in Appendix 1.

Inmunoglobulinas;
Células plasmáticas;
Amiloidosis;
Componente monoclonal

Se revisan las características clínicas y analíticas de los diferentes tipos de gammapatía monoclonal, las guías de consenso internacionales y las técnicas utilizadas para la detección y seguimiento del componente monoclonal.

Background

Monoclonal gammopathies encompass a collection of disorders associated with uncontrolled proliferation of plasma cell clones that, with the exception of nonsecretory myeloma, produce immunoglobulin molecules or their fragments, which are known as monoclonal components (MCs).

There is a diverse spectrum of diseases grouped within monoclonal gammopathies, which is reflected in the clinical manifestations and their prognosis. These diseases are classified as malignant or nonmalignant.

The nonmalignant types include monoclonal gammopathy of undetermined significance (MGUS). In MGUS, the amount of plasma cells detected in bone marrow biopsies is less than 10%, and serum MC levels are less than 30 g/L. MGUS represents 60% of all monoclonal gammopathies and is present in 3.2% of the population around the age of 50 years. MGUS is characterized as benign (lack of anemia, renal failure, hypercalcemia, bone lesions or amyloidosis attributable to plasma cell dyscrasia) and asymptomatic, with an annual risk of progression to multiple myeloma (MM) of 0.5–1%. The risk factors for progression to MM include the MC concentration, the type of monoclonal protein, the light chain ratio, bone marrow plasmacytosis, the proportion of cells with the myelomatous phenotype in the total plasma cell count and the presence of immunoparesis.[1]

MGUS can present in isolation or associated with other underlying diseases: autoimmune (cryoglobulinemia, Sjögren's syndrome, IgA vasculitis), post-transplant immunodeficiencies, liver disease (chronic hepatitis, primary biliary cirrhosis, hepatitis C virus infection), rheumatism (rheumatoid arthritis, systemic lupus erythematosus), hemopathies (purpura fulminans), endocrinopathies (thymoma, Hashimoto's thyroiditis, myxedema), infectious diseases (human immunodeficiency virus infection, septic arthritis, pneumonia) and others (pyoderma gangrenosum).

There are four types of MGUS[2]:

1) IgM MGUS. Some 1–5% of cases progress to Waldenstrom macroglobulinemia or amyloidosis (light chain [AL], heavy chain [AH] or light and heavy chain [AHL]). Less frequently, cases can progress to IgM-secretory MM (abnormal proliferation of IgM-secretory plasma cells located in the bone marrow).
2) Non-IgM MGUS. One percent of cases progress annually to MM. They can also progress to solitary bone plasmacytoma or amyloidosis (AL, AH and AHL).
3) Light-chain MGUS. This condition is defined by an increase in involved free light chain levels, an abnormal light chain ratio and a lack of organ damage. The risk of progression to light-chain secretory MM can reach 3% annually, which can also progress to amyloidosis.
4) Secondary MGUS. This type refers to the development of a new monoclonal protein in the course of a MM and that has an isotype (heavy and/or light chain) different from the original clone (e.g., IgM MGUS in a patient with IgG MM). This condition is more common in patients who have undergone hematopoietic stem cell transplantation and is associated with longer survival.[3]

The malignant monoclonal gammopathies include.

a) MM Represents 1% of all malignancies and 13% of hematological malignancies.[4] Bone marrow plasmacytosis ≥10% or the presence of a plasmacytoma (bone or extramedullary) are characteristics of MM. The presence of a monoclonal protein is not a requirement for diagnosis, because in the so-called nonsecretory myelomas the monoclonal protein is not detected in serum or urine, but its presence or absence is useful for classifying the myelomas. MM is also characterized by the presence of organ damage secondary to the clonal proliferation, which results in the defining events of MM (hypercalcemia, renal failure, anemia and bone lesions), and by the presence of one or more malignancy markers such as ≥60% bone marrow infiltration by plasma cells, ≥100 involved/uninvolved free light chains in serum (FLCs) ratio, or ≥0.1 g/L involved FLCs or more than one focal lesion in magnetic resonance imaging (each lesion must be ≥5 mm).[5]
b) Smoldering MM (SMM). This condition is an intermediate stage between MGUS and MM. The risk of progression to MM is approximately 10% annually during the first 5 years. SMM is defined by the presence of ≥30 g/L serum MC (IgG or IgA) levels, ≥500 mg/24 h urinary monoclonal protein levels or a 10–60% plasma cells in bone marrow, in the absence of organ damage.[5,6]
c) Nonsecretory MM. Represents approximately 3% of MMs. This condition is an MM that is symptomatic and in which the MC is undetectable by immunofixation, both in serum and urine. The percentage of plasma cells in the bone marrow is greater than 10% or there is a plasmacytoma. Many of these cases require confirmation by biopsy.[6–8]
d) Oligosecretory MM. Five to 10% of patients with MM have a oligosecretory MM at the time of diagnosis,[9] as defined by the presence of <0.1 g/L serum monoclonal protein levels or <200 mg/24 h urine monoclonal protein levels. As with nonsecretory MM, these patients need to be monitored by imaging studies and bone marrow tests, especially if the baseline FLC levels are <0.1 g/L or there are questions about the reliability of the results.[6,9]