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Review

Monoclonal gammopathies of renal significance☆

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ABSTRACT

The term monoclonal gammopathy of renal significance (MGRS) comprises a group of diseases pathogenetically characterised by proliferation of a B-cell or plasma cell clone that synthesises and secretes a monoclonal immunoglobulin or its components (light and/or heavy chains), that may deposit and cause glomerular, tubular, interstitial and/or vascular damage. The importance of differentiating the term MGRS from other monoclonal gammopathies lies in the fact that diagnostic and therapeutic procedures aimed at controlling monoclonal protein synthesis and secretion can be indicated, irrespective of the classic criteria based on malignant tumour expansion. Renal pathology associated with MGRS is highly heterogeneous, and therefore renal biopsy should be considered a key diagnostic tool. A precise diagnostic approach, however, must also identify the monoclonal protein in plasma and/or in urine, together with a complete haematological study in order to determine the nature and extension of cell clones. Recent advances in the understanding of these entities have resulted in significant improvements in clinical course and survival in several forms of MGRS, although more studies and clinical experience are needed in order to delineate more effective therapeutic strategies. In this review, we summarise the main clinical and pathological features of MGRS, highlighting the most appropriate diagnostic approach and current therapeutic options.

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Gammapatías monoclonales de significado renal

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RESUMEN

Bajo el término gammapatías monoclonales de significado renal (GMSR) se engloban un conjunto de enfermedades que se caracterizan patogénicamente por la proliferación de un clon de linfocitos B o células plasmáticas que sintetizan y segregan una inmunoglobulina monoclonal o uno de sus componentes (cadenas ligeras o pesadas), con capacidad para depositarse y producir daño a nivel glomerular, tubular, intersticial o vascular. La importancia de discriminar el término GMSR radica en poder indicar procedimientos diagnósticos y terapéuticos dirigidos al control de la síntesis y secreción de las proteínas monoclonales independientemente de los criterios clásicos vinculados con la expansión tumoral maligna. La patología renal asociada a las GMSR es muy heterogénea, lo que confiere a la biopsia renal una consideración de prueba diagnóstica clave. La correcta investigación diagnóstica de una GMSR debe incluir, además, la identificación en plasma u orina de la proteína monoclonal y un estudio hematológico completo que determine la naturaleza y extensión del clon celular. Los avances en el conocimiento de estas entidades han permitido mejorar el curso evolutivo y la supervivencia en varias formas de GMSR, aunque son necesarios más estudios y experiencia clínica para delinear protocolos terapéuticos más efectivos. En la presente revisión se resumen las principales características clínico-patológicas de las GMSR, se detalla la aproximación diagnóstica más adecuada, así como las opciones terapéuticas disponibles en el momento actual.

Introduction

Several clinical entities are grouped under the name monoclonal gammopathies (MGs). They share a clonal proliferation of B-cells or plasma cells with the capacity to produce and secrete large amounts of a unique type of immunoglobulin or a constituent part of it (monoclonal component). The monoclonal component may be constituted of a heavy chain (normally γ chain and, less frequently, α, μ, δ, ε chains) along with a light chain (κ or λ), isolated light chains and, in exceptional circumstances, only heavy chains.[1]

The range of diseases, clinical manifestations and adverse health effects and persistence of entities is not only related to neoplastic cell proliferation, but also to the damage produced by the deposit of these monoclonal proteins in different organs, or through more complex pathogenic mechanisms, including autoimmunity, inflammation and fibrogenesis.[2–4]

In 2003, the International Myeloma Working Group[2] revised the criteria for the diagnosis and classification of the clinical entities that are grouped under the term MG. In accordance with these criteria, there are four different entities:

1. MG of undetermined significance (MGUS): monoclonal component <30 g/l, with proliferation of plasma cells in bone marrow (<10%) and lack of clinical evidence of myeloma, lymphoma or amyloidosis.
2. Asymptomatic or quiescent myeloma: monoclonal component ≥30 g/l, with proliferation of bone marrow plasma cells ≥10%, but without evidence of organs or tissues involvement and, absence of the typical tetrad of hypercalcaemia, renal involvement, anaemia and bone lesions.
3. Symptomatic myeloma which requires involvement of organs or tissues and which can also present as non-secretory (with no secretory component of monoclonal proteins). In 2014, the following additional criteria were incorporated: the presence of ≥60% plasma cells in bone marrow, a involved/uninvolved serum free light chain ratio ≥100, or the existence of more than one focal lesion using advanced imaging techniques (computed tomography [CT], magnetic resonance imaging [MRI] or positron emission tomography with 18F-fluorodeoxyglucose [PET-CT]).[5]
4. Solitary bone plasmacytoma, extramedullary plasmacytoma and multiple solitary plasmacytomas.

Approximately 60% of all MGs are MGUS.[6] In MGUS, a clone of B-cells or plasma cells, which are generally not neoplastic, produces and secretes small quantities of a monoclonal immunoglobulin or its components (light or heavy chains).[7,8]

This entity is a relatively common finding in the adult population (prevalence of 0.7% in the general population, increasing to 3% in those over the age of 50 and to 5% in those above the age of 70),[8] with an annual standardised incidence of 4–15 cases per 100,000 according to different studies,[9,10] but which may peak at 169 cases per 100,000 in individuals older than 80.[10]

It is estimated that in MGUSs there is neoplastic transformation (myeloma or lymphoma) in 1% annually.[11–13] The factors which have proven to be determinant risk factors for neoplastic transformation are the following[11–13]: abnormal kappa (κ) to lambda (λ) free light chains ratio, different monoclonal immunoglobulin component (light or heavy chains) or of IgA type, and monoclonal protein concentration ≥15 g/l. If these three factors are present, the risk of neoplastic