Monoclonal gammopathy of renal significance: a nephrologist's perspective

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Introduction The current diagnostic criteria define monoclonal gammopathy of undetermined significance (MGUS), which is considered a benign plasma cell dyscrasia, include serum M protein levels of less than 3 g/dl and bone marrow infiltration of clonal plasma cells of less than 10%, with no disease-related end-organ damage. Monoclonal gammopathy of renal significance (MGRS) fulfills the hematologic criteria for monoclonal gammopathy defined as a heterogenic group of disorders pathogenetically characterized by proliferation of a B-cell or plasma cell clone. This small clone synthesizes and secretes a monoclonal immunoglobulin (Ig) or its components (light or heavy chains), which may be directly deposited in the kidneys or indirectly cause alternative complement pathway dysregulation and cause glomerular, tubular, interstitial, or vascular damage. The term MGRS does not encompass kidney disorders associated with large clone lymphoproliferative disorders, such as multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, and malignant lymphoma. The prognosis for survival is more severe when compared with MGUS, because if untreated, MGRS leads to progression of kidney damage. Moreover, in MGUS treatment is not necessary, while in MGRS therapy is fundamental and has been shown to improve long-term outcomes.[1,2]

Diagnosis of monoclonal gammopathy of renal significance The diagnosis of a suspected MGRS is based on the presence of kidney damage (progressive kidney failure, nephrotic syndrome and nonnephrotic proteinuria, Fanconi syndrome, or tubulointerstitial dysfunction) in association with monoclonal peak in serum electrophoresis. In most cases, the diagnosis is established using serum and urine electrophoresis, and according to recommendations, a 24-hour urine collection for electrophoresis is required. However, in cases where the concentration of monoclonal protein in plasma or urine is undetectable in conventional electrophoresis, plasma and urine immunofixation must be additionally performed. Immunofixation will identify the type of monoclonal protein and determine whether free light chains are present in blood and urine. Interestingly, most cases of kidney damage in MGRS are diagnosed mainly on the basis of findings in kidney biopsy. Kidney biopsy is required for the diagnosis of MGRS, and must include immunohistochemistry, immunofluorescence, and electron microscopy. Monoclonal Ig deposition is involved in many types of MGRS.[3,4]

Pathological studies may require electron microscopy because it allows a proper characterization of the ultrastructural organization of Ig deposits. Importantly, the diagnosis of amyloid light-chain (AL) amyloidosis requires not only Congo red staining of the biopsied tissue but also immunohistochemistry and immunoelectron microscopy or mass spectrometry. These methods are also used to exclude a late-onset hereditary form of amyloidosis or the wild-type transthyretin. Laser microdissection and mass spectrometry proteomics are recommended to confirm not only AL amyloidosis but also cases of monoclonal Ig deposition disease with truncated monoclonal Ig or types where the specific monoclonal Ig region is of interest. To identify a pathological clone, diagnostic workup should begin with a bone marrow biopsy, which in most cases is sufficient for clonal identification. Flow cytometry is important for identification of smaller clones, which may be often missed by a histologic examination. It is important especially in the presence of clonal plasma cells or B cells, even when marrow cellularity is below 5% of pathological marrow cells. When the bone marrow specimen is negative for atypical plasma cells or B-cells, a lymph node biopsy may be necessary. Positron emission tomography, computed tomography, or magnetic resonance imaging may be helpful in locating adenopathy.[1,5]

Pathogenesis of renal damage in monoclonal gammopathy of renal significance Two major pathophysiological mechanisms have been involved in MGRS: direct and indirect, which mainly depend on physicochemical properties of monoclonal Ig. The direct mechanism is the most common. Here kidney damage is induced by direct monoclonal Ig deposition. It is preceded by receptor-mediated endocytosis into glomerular or tubular cells after monoclonal Ig has been filtered into

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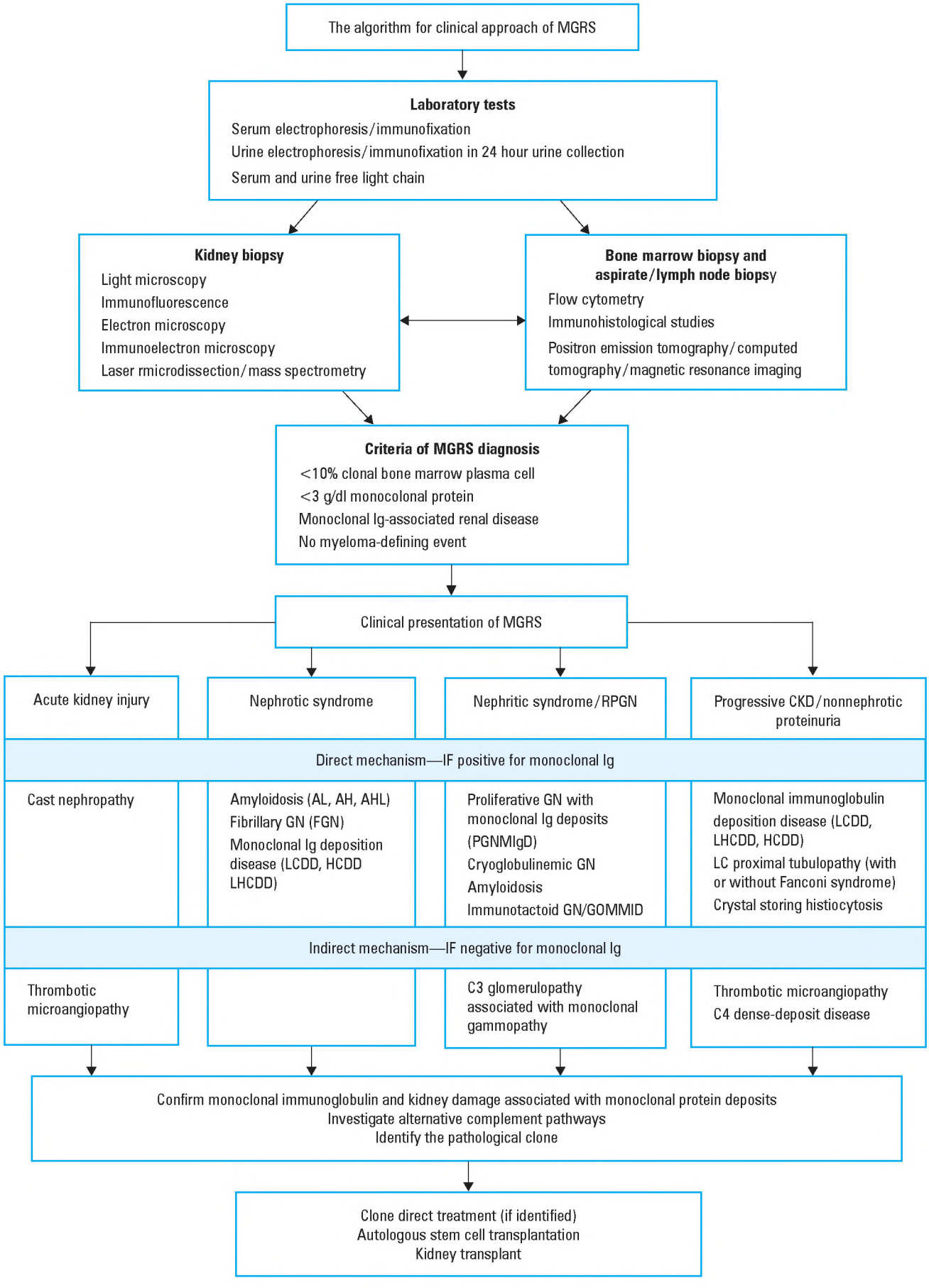

FIGURE 1 Proposed algorithm for nephrologic workup in patients with monoclonal gammopathy of renal significance
Abbreviations: AH amyloidosis, heavy-chain amyloidosis; AHL amyloidosis, heavy- and light-chain amyloidosis; AL amyloidosis, light-chain amyloidosis; GN, glomerulopathy; GOMMID, glomerulopathy with organized microtubular monoclonal deposits; HCDD, heavy-chain deposition disease; LC, light chain; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; MGRS, monoclonal gammopathy of renal significance; MIDD, monoclonal immunoglobulin deposition disease; PGNMIgD, proliferative glomerulopathy with monoclonal immunoglobulin deposits

the urinary space. The indirect mechanism depends on monoclonal Ig acting as an autoantibody, as in the case of C3 glomerulopathy and atypical hemolytic uremic syndrome. Here antibodies influence dysregulation of the liquid or solid phase of the alternative complement pathway; for example, anti–factor H is the main antibody involved in C3. A similar mechanism was also found in C4 dense deposit disease with dysregulation of the mannose-binding lectin pathway of the complement.[2]

The algorithm for the clinical approach to MGRS is presented in FIGURE 1.

Histologic findings The diagnosis of MGRS requires an analysis of morphologic alterations seen on light microscopy, electron microscopy, and immunofluorescence, in correlation with clinical parameters. Immunofluorescence should be performed using panel antibodies specific for different light chains and monoclonal Ig isotypes.

Among the histologic lesions observed in MGRS, we distinguish organized and nonorganized Ig deposits. Examples of organized deposits are fibrillar Ig deposits, amyloidosis, fibrillary glomerulonephritis, microtubular Ig deposits, immunotactoid glomerulopathy, type I cryoglobulinemic glomerulonephritis, and types with crystal inclusion (such as proximal tubulopathy, with or without Fanconi syndrome, and histiocytosis, in which the crystal deposits are not found in tubular epithelial cells but inside the histiocytes). On the other hand, histomorphological lesions include also nonorganized Ig deposits such as proliferative glomerulonephritis with monoclonal IgG deposits, C3 glomerulopathy with monoclonal gammopathy, and monoclonal immunoglobulin deposition disease.[5] Clinical manifestations of the heterogeneous group of diseases occurring in MGRS are presented FIGURE 1.

Treatment of monoclonal gammopathy of renal significance Every case of MGRS should be consulted by a hematologist for eradication of the clonal disease. The most common multidrug treatment regimen that would be appropriate for the clones detected in MGRS disorders includes cyclophosphamide, proteasome inhibitors (bortezomib or carfilzomib), dexamethasone, bendamustine, and rituximab. Immunomodulatory agents (thalidomide, lenalidomide, or pomalidomide combined with dexamethasone) are also prescribed. In the future, anti-D38 monoclonal antibody (daratumumab) can be used for the treatment of newly diagnosed MGRS, as in patients with multiple myeloma. In MGRS caused by the indirect mechanism (such as C3 glomerulonephritis and dense deposit disease), the use of eculizumab may result in the reduction of proteinuria and serum creatinine levels. After hematologic remission in patients with MGRS and end-stage renal disease, autologous stem cell transplantation and kidney transplantation should be considered.[3,4]

MGRS is a disease of the kidney, secondary to a B-cell or plasma cell clonal proliferation or the alternative pathway of complement dysregulation and immune dysfunction. It requires a therapeutic intervention to eradicate the offending clone. Untreated MGRS leads to kidney damage and renal replacement therapy, worsening prognosis and decreasing survival in this patient group.

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