The concept of monoclonal gammopathy of undetermined significance (MGUS) was first introduced in 1978 by Robert Kyle. This premalignant condition is characterized by the presence of a serum monoclonal immunoglobulin <30 g/l and <10% monoclonal bone marrow plasma cells in a patient who does not have any organ damage attributable to the monoclonal immunoglobulin. Conversion of MGUS to malignancy, which mandates the initiation of appropriate treatment, is indicated by the development of disease-specific features. For example, conversion to multiple myeloma (MM) is indicated by the occurrence of one or more myeloma-defining events, such as hypercalcaemia, renal impairment, anaemia, lytic bone lesions or an event suggestive of impending myeloma (such as a serum involved/uninvolved free light-chain ratio >100, >60% bone marrow plasma cells or ≥1 bone lesions on MRI). Progression to Waldenström macroglobulinaemia (WM) is indicated by the development of anaemia, thrombocytopenia, bulky adenopathy or organomegaly, blood hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinaemia, cold agglutinin disease or malignant transformation. Similarly, treatment for chronic lymphocytic leukaemia (CLL) is initiated when a patient with MGUS develops cytopenias, progressive or symptomatic lymphadenopathy, organomegaly or
constitutional symptoms. Patients with MGUS who do not yet exhibit any of these disease-specific features do not require treatment but should undergo careful monitoring. The kidney is commonly involved in these haematological malignancies. Light-chain cast nephropathy is now considered a myeloma-defining event, although it is not exclusive to MM. In addition to cryoglobulinaemic glomerulonephritis, a variety of other kidney diseases have been observed in patients with WM, including immunoglobulin light-chain (AL) amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), light-chain proximal tubulopathy (LCPT) and, on rare occasions, cast nephropathy. Similar renal lesions have also been described in patients with CLL. Importantly, however, these kidney diseases have also been described in patients with a low clonal burden (defined as monoclonal immunoglobulin <30 g/l and <10% monoclonal bone marrow plasma cells) who therefore do not meet the diagnostic criteria for MM or other malignancies. In the past, these patients were categorized as having ‘idiopathic’ light-chain disposition disease or ‘primary’ amyloidosis. The fact that these kidney lesions have been replicated in animal models by Bence Jones protein injections alone further supports the notion that the presence of MM is not required. For this reason, the International Myeloma Working Group does not consider patients with plasma cell dyscrasia and kidney diseases other than cast nephropathy to have MM unless they also exhibit other myeloma-defining events.

The occurrence of kidney diseases associated with a monoclonal gammopathy in the absence of symptomatic MM, WM or CLL is increasingly recognized. Most of these patients have a small, low-grade clonal disorder that is similar to MGUS, although (unlike MGUS) these clones do cause vital organ damage — including neuropathy, cardiomyopathy, hepatic dysfunction and dermopathy — mediated by the monoclonal immunoglobulin. The clonal aetiology of these diseases results in clinical features that differ from those of non-monoclonal gammopathies, such as membranous nephropathy or IgA nephropathy. For example, monoclonal immunoglobulin-related diseases tend to be progressive and are unlikely to undergo spontaneous remission. Monoclonal immunoglobulin-related diseases also show higher rates of recurrence after kidney transplantation (often >80%) than their non-monoclonal counterparts. Monoclonal diseases are poorly responsive to conventional immunosuppression and instead require clone-directed therapy.

Increasing recognition of the relationship between monoclonal gammapathies and kidney disease generated the need for more-accurate classification of these disorders, which were previously often misdiagnosed or categorized as unclassifiable by existing disease criteria. Moreover, as the use of cytotoxic therapy is typically limited to patients with MM, WM or CLL, patients with monoclonal gammopathy-related kidney diseases (who do not meet the criteria for these malignancies) were left without access to these essential drugs. Accordingly, a series of meetings was organized by the International Kidney and Monoclonal Gammapathy Research Group (IKMG) with the aim of designating these clonal disorders as pathologies distinct from MGUS and thereby enabling government agencies to allocate resources for their treatment. In 2012, the IKMG introduced the term monoclonal gammapathy of renal significance (MGRS) to describe haematological conditions that produce a monoclonal immunoglobulin associated with kidney injury. Since then, the IKMG has published recommendations for the treatment of MGRS and a classification scheme for MGRS-related renal lesions. The IKMG met again in New Orleans, Louisiana, United States, in 2017 to update the classification of MGRS-associated renal lesions as well as to refine the definition of MGRS. The present Expert Consensus Document is derived from these discussions, which occurred both face to face and in e-mail exchanges that incorporated the views of IKMG members who could not be present. The treatment of MGRS was not discussed at the meeting; therefore, this topic is not updated in this consensus document.

**Consensus statement**

- **Bence Jones protein**
- **Monoclonal immunoglobulin light chains detected in the urine of patients with multiple haematological malignancies.**

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**Author addresses**

1. Division of Nephrology, Hematology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.
2. Department of Nephrology, Centre Hospitalier Universitaire et Université de Poitiers, Poitiers, France; CNRS UMR7276, Limoges, France; and Centre de Référence Amylose AL et Autres Maladies par Dépôt d’Immunoglobulines Monoclonales, Poitiers, France.
3. Veterans Administration Medical Center, New Orleans, LA, USA and Tulane University Medical School, Tulane, LA, USA.
4. Centre for Haematology, Department of Medicine, Imperial College London and Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK.
5. Department of Nephrology, Renal Medicine — University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, UK.
6. Department of Pathology, Renal Pathology Laboratory, Columbia University, College of Physicians and Surgeons, New York, NY, USA.
7. Department of Haematology and Immunology, University Hospital St Louis, Paris, France.
8. The Victorian and Tasmanian Amyloidosis Service, Department of Haematology, Monash University Eastern Health Clinical School, Melbourne, Victoria, Australia.
9. National Amyloidosis Centre, Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, Royal Free Campus, University College London, London, UK.
10. Department of Pathology and Translational Pathobiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA.
11. Service d’Hématologie et de Thérapie Cellulaire, Centre de Référence des Amyloses Primitives et des Autres Maladies par Depots d’Immunoglobuline, CHU Limoges, Limoges, France.
12. Department of Clinical Therapeutics, School of Medicine National and Kapodistrian University of Athens Alexandra Hospital, Athens, Greece.
13. University Health Network, Princess Margaret Cancer Centre, Toronto, Canada.
14. Arkana Laboratories, Little Rock, AR, USA.
15. Wilhelminen Cancer Research Institute, Wilhelminenspital, Vienna, Austria.
16. Amyloidosis Research and Treatment Center, IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy.
17. Haematology Department, Princess Alexandra Hospital and School of Medicine, University of Queensland, Brisbane, Australia.
18. Department of Pathology, Loyola University Medical Center, Maywood, IL, USA.
19. Department of Pathology, Hôpital Maisonneuve-Rosemont, Université de Montreal, Montreal, Quebec, Canada.
20. Department of Medicine, University of Alabama at Birmingham and Department of Veterans Affairs Medical Center, Birmingham, AL, USA.
21. Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada.
22. Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium System, Charlotte, NC, USA.
23. Abramson Cancer Center, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA.

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Updated definition of MGRS

The original definition of MGRS included all small B cell clones that produced a toxic monoclonal protein. Although this definition was based on the dangerous small B cell clones concept, the nature of the clonal disease was not well defined. Specific criteria arose regarding whether patients with smouldering (indolent) MM (SMM) or smouldering (indolent) WM (SWM) should be considered to have MGRS. Similar confusion existed with regard to the inclusion of patients with low-grade CLL or lymphoma, who do have a diagnosis of a malignancy but do not require treatment. The new definition includes all B cell and plasma cell clonal proliferative disorders that do not require immediate treatment for the clonal disease. In addition, the toxic monoclonal protein is now specified to be a nephrotoxic monoclonal immunoglobulin.

The new IKMG consensus definition of MGRS (Box 1) includes all B cell or plasma cell clonal proliferative disorders (such as SMM, SWM and monoclonal B cell lymphocytosis (MBL; a diagnosis that is the equivalent of MGUS for clones of the CLL lineage)) that produce a nephrotoxic monoclonal immunoglobulin. Low-grade CLL and low-grade B cell non-Hodgkin lymphomas, such as marginal zone lymphoma, mantle-cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma are also considered to be MGRS when they are associated with renal lesions (Table 1). These low-grade proliferative disorders would be classified as MGUS, and affected patients would be monitored for progression but not offered treatment if not for the renal injury. In patients who develop renal lesions as a result of the monoclonal immunoglobulin, therapeutic intervention is required to prevent further damage resulting in end-stage renal disease. Accordingly, the diagnosis of MGRS does not require the presence of any defining features of an overt lymphoplasmacytic malignancy and particularly not the presence of any myeloma-defining event.

Once the haematological condition progresses to overt MM, WM, advanced stage CLL or malignant lymphoma (as defined by their respective established disease criteria), these diseases are no longer considered MGRS and affected patients are managed according to disease-specific protocols.

Updated classification system

Terminology. A variety of renal diseases have now been described in association with MGRS. The IKMG recommends that these should be referred to as MGRS-associated lesions, conditions or disorders. Thus, for instance, classic AL amyloidosis might be considered an MGRS-associated condition when renal involvement is present. By contrast, the term MM-associated AL amyloidosis would be used when the same renal condition is associated with a symptomatic high tumour mass accompanied by at least one classic myeloma-defining event.

The type of renal lesion is governed by the innate structural characteristics and physicochemical properties of the monoclonal immunoglobulin rather than by the features of the clone that produced it. Except for C3 glomerulopathy and thrombotic microangiopathy, which are not associated with renal deposition of monoclonal immunoglobulin, most MGRS-associated lesions are caused by the deposition of entire or parts of the monoclonal immunoglobulins or of various products of aggregation. Monoclonal immunoglobulin deposits in the kidney are generally restricted to immunoglobulin light chains (except in diseases that show a monoclonal immunoglobulin heavy-chain restriction, such as heavy-chain deposition disease or immunoglobulin heavy-chain amyloidosis). For example, in AL amyloidosis, the renal deposits are composed of only a single light chain. In conditions where the entire immunoglobulin is deposited, demonstration of both heavy-chain and light-chain restrictions are required to provide evidence of monoclonality.

The classification scheme proposed in 2017 by the IKMG for MGRS-associated lesions is based on the findings of immunofluorescence studies and the ultrastructural appearance of the deposits on electron microscopy. However, electron microscopy is not universally available, even in industrialized countries; consequently, the IKMG classification encourages but does not mandate the use of electron microscopy in the assessment of MGRS-associated disorders. By contrast, light microscopy and immunofluorescence studies with a full panel of antibodies are invariably required. The renal deposits are initially categorized as organized, non-organized and non-immunoglobulin. At the 2017 IKMG meeting in New Orleans, two additional subcategories were added to the non-organized and non-immunoglobulin categories of the classification scheme. Thrombotic microangiopathy associated with monoclonal gammopathy was provisionally added as a subcategory of non-immunoglobulin deposits, and a miscellaneous subcategory was added to the non-organized deposit category, which applies to pathological entities that are ultrastructurally similar to a non-monoclonal-immunoglobulin-related disease but are only sometimes associated with a monoclonal gammopathy. The MGRS-associated disorders included in this classification are discussed in more detail below.

Lesions with organized deposits. Organized deposits of monoclonal immunoglobulins can be further divided into fibrillar, microtubular or crystalline and/or inclusionary forms. Immunoglobulin-related amyloidosis, which includes subtypes with light-chain, heavy-chain and both heavy- and light-chain deposition
### Table 1: Characteristics of clonal B cell and plasma cell proliferative disorders

| Disease | Clone | Bone marrow involvement | Immunoglobulin | M-spike | Organ damage and/or involvement |
|---------|-------|-------------------------|----------------|---------|--------------------------------|
| MGUS    | Any   | <10%                    | Any            | <30 g/l | None                            |
| Smouldering MM    | Plasma cell | 10–60% | Any            | ≥30 g/l | None                            |
| MM    | Plasma cell | ≥10% | Any            | ≥30 g/l | SLIM CRAB: 60% bone marrow plasma cells, involved/uninvolved free light-chain ratio >100, >1 bone lesion on MRI, hypercalcaemia, renal impairment, anaemia and lytic bone lesions |
| Smouldering WM    | Lymphoplasmacytic lymphoma clone | ≥10% | IgM            | ≥30 g/l | Absent |
| WM    | Lymphoplasmacytic lymphoma clone | ≥10% | IgM            | ≥30 g/l | Anaemia, hyperviscosity, constitutional symptoms, bulky lymphadenopathy, hepatosplenomegaly and neuropathy |
| MBL    | B-cell clone | Peripheral B-cell count <5 × 10^9/l | Any | Any | Absence of lymph node involvement |
| CLL    | B-cell clone | Peripheral B-cell count >5 × 10^9/l | Any | Any | Adenopathy, anaemia and thrombocytopenia |
| Other B cell lymphoproliferative disorders | Pan B-cell markers (CD19+CD20+CD79a+PAX5+) | Presence or absence | Any | Any | Adenopathy and splenomegaly |

**Note:**
- CLL, chronic lymphocytic leukaemia; MBL, monoclonal B cell lymphocytosis; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SLIM CRAB, symptomatic, light chains, MRI, high calcium, renal dysfunction, anaemia, and bony lytic lesions; WM, Waldenström macroglobulinaemia.
- Either bone marrow involvement or an M-spike above these thresholds is sufficient for the diagnosis.
- Typically, B cells are surface IgM+CD5+CD10−CD23−CD11c+ surface immunoglobulin.

(AL, AH and AHL, respectively), has traditionally been recognized as the only condition in the fibrillar category\(^5\). However, monoclonal fibrillary glomerulonephritis has occasionally also been reported\(^5\). Amyloid fibrils stain with Congo red and are solid, non-branching and randomly arranged, with diameters of 7–12 nm (Fig. 3a). Amyloid fibrils involve glomeruli and blood vessels in the vast majority of patients and the interstitium in roughly 60% of patients (Fig. 2). Intratubular cytoplasmic AL amyloidosis occurs rarely\(^5\). The randomly arranged fibrils seen in fibrillary glomerulonephritis are on average twice as thick (10–30 nm) as those observed in amyloidosis (Fig. 3b) and generally do not stain with Congo red\(^5\). A small subgroup (7–17%) of patients with fibrillary glomerulonephritis demonstrates clinical evidence of a monoclonal gammopathy. In 3–15% of these patients, the IgG deposits exhibit light-chain restriction\(^5,46,47\), and this pathology is termed monoclonal fibrillary glomerulonephritis. Glomerular staining for Dna J homologue subfamily B member 9 (DNAJB9) is a reliable marker for fibrillary glomerulonephritis\(^48\). This feature can be used to distinguish monoclonal fibrillary glomerulonephritis from AH and AH amyloidosis, especially as fibrillary glomerulonephritis can sometimes show Congo red staining\(^49,50\).

Immunotactoid glomerulonephritis and cryoglobulinaemic glomerulonephritis are the two diseases that feature microtubular immunoglobulin deposits (Fig. 3c). Microtubules can be distinguished from fibrils by their hollow centres and large diameters (17–52 nm)\(^51\). Only type I and II cryoglobulinaemias are considered to be MGRS-associated disorders because type III cryoglobulinaemia is associated solely with polyclonal immunoglobulins. Immunotactoid glomerulonephritis is usually a renal-limited disease, whereas systemic manifestations including vasculitic rashes, peripheral neuropathy and arthralgias are common in patients with cryoglobulinaemia. Moreover, immunotactoid glomerulonephritis is not associated with cryoglobulinaemia and does not display the typical characteristics of cryoglobulinaemic glomerulonephritis (namely, glomerular protein thrombi and arterial or arteriolar vasculitic lesions). The glomerular deposits in immunotactoid glomerulonephritis are uniformly composed of microtubules, typically arranged in parallel arrays, with predominantly subepithelial and subendothelial localization. By contrast, only some of the deposits in cryoglobulinaemic glomerulonephritis are organized, and they usually appear as short, curved or straight microtubules (Fig. 3d) with predominantly intraluminal and subendothelial localization\(^52\). Of note, organized deposits are not always observed in cryoglobulinaemic glomerulonephritis\(^53\).

The crystalline and/or inclusions category consists of LCPT, crystal-storing histiocytosis (CSH) and (cryo) crystalglobulinaemic glomerulonephritis\(^54,57\). LCPT occurs as crystalline and non-crystalline variants. In the crystalline variant, numerous light-chain crystals of various shapes are seen within proximal tubular cells, inside lysosomes or freely in the cytoplasm (Figs 1, 3e). This variant is associated with x light-chain deposition and complete or partial Fanconi syndrome\(^55\). In the non-crystalline variant, proximal tubular cells are...
distended and injured by the accumulation of numerous non-crystalline light-chain inclusions within lysosomes. This variant is typically associated with λ rather than κ light-chain deposition, and Fanconi syndrome is uncommon. Rarely, non-crystalline LCPT can mimic acute tubular necrosis or acute interstitial nephritis. In patients with CSH, light-chain crystals are often seen in renal histiocytes as well as in proximal tubular cells and can have a widespread extrarenal distribution, including in bone marrow, lymph nodes, lungs, thyroid, parotid gland, cornea, synovium, skin, subcutaneous fat, stomach, liver and brain. Finally, (cryo)crystalglobulinemic glomerulonephritis is a rare monoclonal gammopathy characterized by immunoglobulin thrombi in
the arterioles and glomerular capillaries. These thrombi exhibit a crystalline structure or periodicity on electron microscopy. In some patients, the crystallization process in the periphery is precipitated by cold exposure, termed cryocrystalglobulinaemia. Mesangial and endocapillary hypercellularity is often absent. As in cryoglobulinemia, intravascular crystal deposition results in small-vessel occlusion, thrombosis and/or inflammatory
Renal biopsy samples in patients with (cryo) crystalglobulinaemia reveal large extracellular crystals within glomerular capillaries and arterioles, which are frequently associated with fibrin thrombi and inflammation. Intracellular crystals can also be seen in patients with cryocrystalglobulinaemia (Fig. 5g).

Lesions with non-organized deposits. Non-organized monoclonal immunoglobulin deposits are seen in patients with MIDD and those with proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID). MIDD comprises a group of diseases characterized by deposition of light chains, heavy
chains or both light and heavy chains. In MIDD (Figs 1, 3), linear punctate deposits are seen along both the glomerular basement membrane (GBM) and the tubular basement membrane (and occasionally extrarenally). By contrast, in PGNMID, deposits are confined to the glomeruli, where they are present in the mesangium and subendothelial space and occasionally in the subepithelial space (Figs 1, 3). In addition, the deposits seen in PGNMID contain only intact immunoglobulins, whereas those seen in heavy-chain MIDD or light-and-heavy-chain MIDD typically lack the first constant domain of the immunoglobulin. In most patients, PGNMID is IgG3-driven, whereas truncated IgG1 is the most frequent immunoglobulin deposited in heavy-chain MIDD. However, PGNMID can also be IgA-driven or (rarely) IgM-driven.

Lesions without deposits. Not all MGRS-associated renal lesions include monoclonal immunoglobulin deposits. The best example of an MGRS-associated disorder lacking such deposits is C3 glomerulopathy with monoclonal gammopathy, which includes both C3 glomerulonephritis and the rare entity of dense deposit disease. By definition, substantial renal immunoglobulin deposits will be absent in patients with C3 glomerulopathy, although 60–80% of patients aged >50 years with C3 glomerulopathy have a monoclonal gammopathy at the time of diagnosis. This proportion far exceeds the expected rate in the general population. Thus, although renal disease related to the monoclonal immunoglobulin can be demonstrated in only about 30% of patients affected by C3 glomerulopathy (in whom the monoclonal immunoglobulin acts as a C3 nephritic factor or anti-factor-H antibody), it should still be considered an MGRS-associated disorder.

C3 glomerulonephritis and dense deposit disease are distinguished by their ultrastructural appearance: ill-defined, moderately electron-dense mesangial, subepithelial and subendothelial deposits are seen in C3 glomerulonephritis (Fig. 3), whereas highly electron-dense ‘sausage-like’ intranembranous deposits and mesangial rounded nodular deposits are seen in dense deposit disease (Fig. 3h). Large ‘hump-shaped’ subepithelial deposits might be seen in either lesion (Fig. 3i). C3 glomerulonephritis is the most common form of C3 glomerulopathy with monoclonal gammopathy. Importantly, roughly 5–10% of patients with monoclonal gammopathy and findings on standard immunofluorescence (that is, conducted on frozen tissue) consistent with C3 glomerulonephritis will actually have a membranoproliferative glomerulonephritis with masked monoclonal deposits. These patients require additional immunofluorescence studies to be performed on protease-digested, paraffin-embedded tissue for identification of the monoclonal immunoglobulin in the deposits.

Lesions with provisional status. Thrombotic microangiopathy is the endothelial injury seen most commonly in microangiopathy with haemolytic anaemia (MAHA). Thrombotic microangiopathy and MAHA can occur concurrently in patients with monoclonal gammopathies, including MM and WM.

The pathophysiology of these disorders is not entirely understood but might be related to the monoclonal immunoglobulin acting as a autoantibody against a complement regulatory protein. The other lesion in this category is glomerular microangiopathy associated with polynuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome. The glomerular microangiopathy seen in POEMS syndrome is associated with a monoclonal gammopathy, which is nearly always light-chain type. However, the light-chain itself is usually absent from kidney biopsy samples. Instead, the lesion is a subacute to chronic glomerular thrombotic microangiopathy characterized by mesangial and endothelial cell proliferation, mesangiolysis, widening of the subendothelial zone and double contouring. Interestingly, these patients show no evidence of MAHA. The renal lesions in POEMS syndrome are thought to be secondary to a cytokine-mediated endothelial cell injury, similar to that seen in myeloproliferative neoplasm-related glomerulopathy.

Lesions classed as miscellaneous. The ‘miscellaneous’ subcategory of MGRS-associated lesions includes kidney diseases that are typically not associated with MGRS, such as anti-GBM disease secondary to a monoclonal gammopathy. The anti-GBM monoclonal antibody can be IgG or IgA. In most patients with this disease, the anti-GBM antibody is not detectable in serum by commercially available enzyme-linked immunosorbent assay (ELISA) or multiplex flow immunoassays, which are designed to detect antibodies against only α3NC1. These patients experience frequent relapses and the disease recurs after kidney transplantation, which is not typical in patients with non-MGRS-associated anti-GBM disease. A pattern of membranous nephropathy that is visually indistinguishable from that associated with polyclonal immunoglobulin-mediated membranous lesions on light microscopy and electron microscopy has been described in patients with monoclonal IgG deposits. Although the phospholipase A2 receptor (PLA2R) was identified as the target of the monoclonal IgG in a single patient included in a small study, a larger study found that only 26% of patients showed evidence of antibodies to PLA2R and that none of those patients had a lymphoproliferative disorder. Finally, Henoch–Schönlein purpura with IgA nephropathy has very occasionally been reported in patients with IgA monoclonal gammapathy or MM.

Evaluation of suspected MGRS. Owing to differences in clinical characteristics and therapy, it is essential to distinguish MGRS-associated disorders from kidney diseases that are unrelated to monoclonal immunoglobulins. In patients suspected of having MGRS, the evaluation starts with a kidney biopsy. If analysis of the biopsy sample identifies an MGRS-associated lesion, a haematological evaluation (including monoclonal immunoglobulin studies, clonal determination and cytogenetic analysis) should be performed. These steps are discussed in greater detail below.
When to perform a renal biopsy. As MGRS is a haematological condition defined by its renal manifestations, a kidney biopsy is essential for its diagnosis. However, not every patient with a monoclonal gammopathy and kidney disease has MGRS. The frequency of MGUS is 3% in people aged >50 years, 5% in persons aged >70 years and as high as 8% in men aged >80 years. The prevalence of MGUS is two to three times higher in African Americans than in white individuals of the same population. The incidence of chronic kidney disease (CKD) also increases after age 60 years. Therefore, the same patient could have both MGUS and CKD that are unrelated to each other. Studies from the same county in the United States found that the annual incidence of glomerular disease was approximately 1 per 100,000 individuals in the general population and that the prevalence of MGUS in people aged >50 years was 3.2%. A renal biopsy study of patients with clinically suspected MGUS found that 45% of these patients did not have an MGRS-associated kidney disorder; however, as additional disease entities related to monoclonal gammopathies have been identified after the publication of this article, the true value might be lower.

Clinicians must balance the risks associated with underdiagnosis of potentially treatable conditions against those of complications from the biopsy procedure. However, patients with MGRS-associated renal lesions (including amyloidosis) do not experience any increase in the risk of bleeding after kidney biopsy (which remains about 4%) Thus, performing a kidney biopsy in a patient with diabetes and rapidly progressive loss of renal function or increasing proteinuria is reasonable, especially if their diabetes is well controlled and/or evidence of extrarenal microvascular disease is absent. Because MGUS is uncommon in individuals aged <50 years (and is especially rare in those aged <40 years), its presence in people aged <50 years, when accompanied by renal manifestations, deserves a thorough evaluation. Older age (≥70 years) should not discourage biopsy as most MGRS-related renal diseases occur in patients aged >50 years. In young and physically fit patients who are eligible for kidney transplantation, a kidney biopsy should be performed provided the kidneys are not markedly shrunken. Transjugular kidney biopsy is an option in high-risk patients from whom it would otherwise be difficult to obtain kidney tissue.

Renal biopsy evaluation. The diagnosis of MGRS-associated lesions requires the integration of morphological alterations seen on light microscopy with the findings of immunohistochemistry (immunofluorescence or immunoperoxidase) and transmission electron microscopy studies, as well as correlation with the patient’s medical history and laboratory findings. In some patients, ancillary techniques are needed to establish the diagnosis, including protease immunofluorescence, ultrastructural immunogold labelling and laser microdissection followed by liquid chromatography and mass spectrometry (LC–MS). A detailed description of our consensus recommendations for renal biopsy and the indications for ancillary techniques is provided in Table 2. Our recommended approach to renal biopsy analysis in patients suspected to have MGRS is provided in Fig. 4.
Consensus recommendations for the evaluation of MGRS-associated disorders

**Table 2 | Consensus recommendations for the evaluation of MGRS-associated disorders**

| Modality                              | Recommendations                                                                                     | Refs |
|---------------------------------------|------------------------------------------------------------------------------------------------------|------|
| **Kidney biopsy**                     | Recommended in the following patients:                                                            | NA   |
|                                       | - Those with monoclonal gammopathy and unexplained kidney disease                                  |      |
|                                       | - Those with known risk factors for chronic kidney disease but an atypical clinical course          |      |
|                                       | - Patients with kidney disease and monoclonal gammopathy aged <50 years                            |      |
| **Protease immunofluorescence on kidney biopsy** | Recommended in the following scenarios:                                                           | NA   |
|                                       | - When glomeruli are lacking in frozen tissue samples                                              |      |
|                                       | - In patients with suspected LCPT and other forms of crystalline nephropathies, such as CSH and    |      |
|                                       |   crystalglobulin-induced nephropathy                                                                |      |
|                                       | - In patients with a monoclonal gammopathy in whom kidney biopsy samples show C3 glomerulonephritis |      |
|                                       |   or unclassified proliferative glomerulonephritis in the context of negative findings by         |      |
|                                       |   immunofluorescence on frozen tissue samples (including in patients with features of            |      |
|                                       |   cryoglobulinaemic glomerulonephritis on light or electron microscopy                              |      |
|                                       | - In patients with fibrillary glomerulonephritis who have apparent light-chain restriction detected |      |
|                                       |   by immunofluorescence on frozen tissue                                                           |      |
| **Renal amyloid typing by liquid chromatography and mass spectrometry** | Recommended in the following situations:                                                          | 108  |
|                                       | - When frozen tissue for immunofluorescence is not available                                        |      |
|                                       | - Negative immunofluorescence staining for κ and λ light chains, with negative immunoperoxidase   |      |
|                                       |   staining for SAA and LECT2                                                                       |      |
|                                       | - Equal staining for κ and λ light chains by immunofluorescence                                     |      |
|                                       | - Bright staining for IgG and/or IgA by immunofluorescence                                           |      |
|                                       | - Equivocal Congo red staining                                                                    |      |
|                                       | - To enable distinction between AHL amyloidosis and congophilic fibrillar gomerulonephritis        |      |
| **Flow cytometry or other immunotyping** | Neoplastic plasma cells frequently show aberrant loss of CD45 and CD19, as well as aberrant        | 118  |
|                                       |   expression of CD56 and CD117; therefore, these markers (in addition to κ and λ light chains and |      |
|                                       |   CD38) are useful in identifying small plasma cell clones                                           |      |
|                                       | - Including CD5 and CD20 in the immunophenotyping of B cells can frequently separate small clones   |      |
|                                       |   from polytypic cells                                                                              |      |
|                                       | - The most sensitive assay available at a given institution should be used.                        |      |
|                                       |   Although there is no established gold standard, many laboratories have the capability to        |      |
|                                       |   determine minimal residual disease in MGRS at a sensitivity of 10⁻⁴ to 10⁻⁶ monoclonal cells.     |      |
|                                       |   The sensitivity of flow cytometry immunophenotyping depends on the total number of collected     |      |
|                                       |   cells, the number of antibodies used to find an aberrant phenotype, the                         |      |
|                                       |   phenotype of the abnormal clone and sample quality                                               |      |
| **Immunohistochemistry**              | Immunohistochemistry of bone marrow biopsy samples has a low sensitivity for detecting κ-expressing  | NA   |
|                                       |   and λ-expressing plasma cells and could be useful only if there is a major plasma cell clone and  |      |
|                                       |   a lack of polyclonal plasma cells                                                                 |      |
|                                       | - Immunohistochemistry might be useful in the evaluation of atypical lymphoid infiltrates,        |      |
|                                       |   particularly if flow cytometry is not available or infiltrates are very focal                     |      |
|                                       | - If an abnormal clone is detected, the light-chain isotype should be compared with that present in |      |
|                                       |   renal lesions and additional information should be obtained                                       |      |
| **Mutational analysis**               | The MYD88 L265P mutation is found in over 90% of patients with lymphoplasmacytic lymphoma or        | 119–121 |
|                                       |   Waldenström macroglobulinaemia but in only 40–60% of individuals with IgM MGUS                   |      |
| **FISH**                              | Cyclin D1 FISH with immunostaining for CD10, BCL2 and BCL6 to subclassify diffuse large cell       | 119–121 |
|                                       |   lymphoma, and prognostic FISH panels for MM and CLL, can also be useful                           |      |

**Abbreviations:** MIDD, LCPT and CSH, by confirming the location and composition of monoclonal deposits, but it is not widely available. Laser microdissection followed by LC–MS is currently the gold standard for amyloid typing but is available in only a few specialized centres. In renal pathology laboratories that routinely perform immunofluorescence studies on native kidney biopsy samples, LC–MS is essential for typing renal amyloidosis in about 15% of patients. LC–MS is crucial for the diagnosis of rare hereditary forms of renal amyloidosis that cannot be typed by immunofluorescence, but it is also important to distinguish AH and AHL amyloidoses from non-immunoglobulin amyloidoses associated with nonspecifically entrapped immunoglobulins (particularly AA amyloidosis) and from fibrillary glomerulonephritis. LC–MS can also be useful in the diagnosis of MGRS-associated lesions other than immunoglobulin amyloidosis when immunofluorescence studies are not available or have negative findings. An example of the latter situation is IgD heavy-chain deposition disease, which is generally missed by immunofluorescence studies because an IgD antibody is not included in the routine immunofluorescence panel.

Monoclonal immunoglobulin testing. Once the diagnosis of an MGRS-associated lesion has been established, a search for the culprit monoclonal immunoglobulin should be undertaken (if it has not been identified already). Protein electrophoresis analyses of serum and urine samples are the first tests performed. Although its sensitivity is inferior to that of some other tests discussed
here, serum protein electrophoresis is quantitative, easy to perform and inexpensive. Urine protein electrophoresis is less sensitive than serum protein electrophoresis but provides the total protein level, urinary albumin level and globular protein (monoclonal immunoglobulin or light chain) component — parameters that are necessary for diagnosis, prognostication and response assessment.\(^{12-14}\). Immunofixation of a serum sample and of a concentrated urine aliquot from a 24 h collection should also be done because this test is more sensitive than protein electrophoresis. Immunofixation is necessary for the identification and typing of monoclonal immunoglobulins, as well as for the determination of a complete response.\(^{11,13}\). Immunoblotting is a highly sensitive technique that can detect small amounts of monoclonal immunoglobulin, characterize the distribution of IgG heavy-chain subclasses and detect deletion of the first constant domain, the hallmark of heavy-chain deposition disease and AH amyloidosis.\(^{70}\). However, this technique is not widely available.

Another critical test is the serum free light-chain assay, which detects unbound free light chains.\(^{113}\). This assay measures κ and λ free light chains independently and can be used to determine the κ:λ free light-chain ratio. Clonality can be inferred from an abnormal κ:λ free light-chain ratio: a high ratio indicates a κ clone whereas a low ratio indicates a λ clone. Because free light chain...
chains are cleared by the kidney, impaired renal function alters the free light-chain concentration. The ‘normal’ free light-chain ratio, 0.26–1.65, can rise to 0.34–3.10 in patients with severe renal impairment (CKD stage 5 or greater), but small declines in renal function can also impair free light-chain clearance\(^{15}\). Knowing which serum free light-chain assay is being used by the laboratory is extremely important, as at least two major assays are currently on the market. Not only are the results of these assays mathematically inconvertible, but the effects of renal impairment differ between these assays; the evidence suggests that the N Latex assay is less affected than the FreeLite assay by impaired renal function\(^{17}\). Thus, the same assay must be used to monitor a particular patient throughout their treatment. Moreover, given that the two assays have different performance characteristics, free light-chain levels might need to be checked using the other assay if the first result is negative. In addition, serum immunofixation might be more helpful than serum free-light-chain assays in diseases associated with an intact monoclonal immunoglobulin (such as PGNMID)\(^{72}\). Finally, although antibodies for use in urinary light-chain assays have been developed, these assays have not been validated and should not be used to quantify the amount of light chain (Bence Jones protein) in a 24 h urine specimen (which should instead be measured by urine protein electrophoresis, as previously stated)\(^{15}\).

Identification of the culprit monoclonal immunoglobulin has important diagnostic and prognostic consequences. The monoclonal immunoglobulin detected in serum and/or urine must match that found in immunoglobulin deposits in the kidney\(^{85}\); if the immunoglobulin found in renal deposits differs from that found in the circulation, the monoclonality of the putative culprit immunoglobulin is called into question. Although the serum M-spike concentration and serum free-light-chain assay results have both diagnostic and prognostic importance, the correlation between the results of these tests and the severity or type of kidney disease is less well established.

### Clonal identification

The diagnosis of MGRS should generally be established before obtaining a haematological consultation. The focus of the haematologist and/or oncologist and haematopathologists should be clonal identification, which is central to the management of patients with MGRS. The only exception is when the patient has already been diagnosed as having MM, WM or CLL, which eliminates the need for a kidney biopsy (because treatment will be initiated regardless of the kidney lesions present). Clonal identification is essential because the same kidney diseases can occur in different haematological disorders (Table 3). Of note, although a pathological clone can be identified in virtually every patient with AL amyloidosis or MIDD, such clones are often difficult to detect in other diseases. For example, the chance of identifying the pathological clone falls below 17% for patients who do not have a detectable monoclonal immunoglobulin on immunofixation studies\(^{2}\), and only 20–30% of patients with PGNMID have a detectable circulating monoclonal immunoglobulin\(^{15}\). As treatment differs according

| Table 3 | Renal lesions associated with monoclonal gammopathy |
|---------|-----------------------------------------------|
| Lesion                          | Proportion of lesions (%) |
|                                | Monoclonal immunoglobulin deposits | Detectable monoclonal immunoglobulin | MM | MGRS | Other\(^a\) | Refs |
| Light-chain cast nephropathy    | 100 | 100 | 99 | 0 | ~1 | 2,4,13,15 |
| Immunoglobulin-related amyloid amyloidosis | 96 | 99 | 16 | 80 | 1–4 | 4,13,13,13,13,13,18,139 |
| MIDD                            | 100 | 100 | 0–20 | 78–100 | 1–2 | 28,32,66,93,131 |
| Light-chain proximal tubulopathy | 100 | 97\(^b\) | 12–33 | 61–80 | 3–8 | 32,66,32,132 |
| Cryoglobulaemic (type I) glomerulonephritis | 100 | 90–100 | 6–8 | 47–52 | 24–56 | 133–136 |
| Cryoglobulaemic (type II) glomerulonephritis | 100 | 49 | 0 | 20 | 7 | 133–136 |
| PGNMID                          | 100 | 30–32 | 4 | 96 | ~1 | 24,72 |
| Crystal-storing histiocytosis   | 83 | 90 | 33 | 8 | 50 | 137 |
| Cryocrystalglobulin or crystalglobulin nephropathy | 91 | 82 | 61 | 18 | 4 | 118 |
| Immunotactoid glomerulonephritis | 69–93 | 63–71 | 0–13 | 25–50 | 25–50 | 23,51 |
| C3 glomerulopathy with monoclonal gammopathy\(^c\) | 0 | 28–83\(^d\) | 0–40\(^d\) | 40–90 | 6–10 | 23,33,75,104 |
| Monoclonal fibrillary glomerulonephritis\(^e\) | 100 | 7–17 | 0–54 | 55–98 | 2–10 | 4,47,119 |

MGRS, monoclonal gammopathy of renal significance; MIDD, monoclonal immunoglobulin deposition disease; MM, multiple myeloma; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits. \(^a\)Haematological conditions including lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia), smouldering Waldenström macroglobulinaemia, B cell lymphomas, chronic lymphocytic lymphoma and monoclonal B cell lymphocytosis. \(^b\)Sensitivity increased by immunofluorescence after pronase digestion. \(^c\)Most instances of fibrillary glomerulonephritis and C3 glomerulopathy are not associated with a monoclonal gammopathy. The percentages for MM, MGRS and other haematological conditions relate to the group of patients who do have a monoclonal gammopathy. \(^d\)Patients over the age of 50 years. \(^e\)In these patients, the glomerular deposits show light-chain restriction or stain for IgG without light chains, both by frozen tissue and paraffin tissue immunofluorescence (as in 15–17% of patients with fibrillary glomerulonephritis).
to whether the clone has a plasmaemic or lymphocytic nature, choosing the right agent is challenging if a clone cannot be identified.

Bone marrow aspiration and biopsy should be performed to evaluate MGRS in most patients, although in patients with CLL clones, the diagnosis could be made with peripheral blood flow cytometry. Morphological assessment should include quantification of the percentage of plasma cells (in plasma cell clones) and evaluation for the presence of atypical lymphoid or lymphoplasma-aggregates (in lymphoma clones) as well as amyloid deposits. In addition, ancillary studies — in particular, flow cytometry immunophenotyping, detection of minimal residual disease and cytogenetic and genetic evaluation of the clones — are helpful for the identification of small clones as well as for deriving treatment recommendations. The myeloma fluorescent in situ hybridization (FISH) panel has shown increasing importance in guiding the treatment of patients with plasma cell dyscrasias. For example, patients with AL amyloidosis featuring translocation (t(11;14)) have inferior responses to bortezomib-based therapy, whereas those with gain of chromosome 1q21 show poorer responses to melphalan plus dexamethasone (versus patients without these genetic variants). These findings highlight the importance of performing the myeloma FISH panel on all bone marrow biopsy samples from patients with plasma cell dyscrasia.

If bone marrow evaluation does not reveal a clonal haematological disorder, the next step could be to perform imaging studies (such as CT with or without PET, or whole-body MRI) to look for a localized plasmacytoma or for lymphoproliferative in low-stage, low-grade lymphoma. For patients suspected to have MM, whole-body CT with or without PET or MRI should be performed to look for bone disease. Any suspicious lesions should be biopsied and enough material should be obtained to enable diagnostic and prognostic studies. Next-generation flow cytometry has been used in the measurement of minimal residual disease. This technique might be helpful in patients suspected of having MGRS who have negative findings on traditional cytology or flow cytometry studies of bone marrow samples.

Summary

MGRS is a new classification of pathogenic clonal proliferative disorders that produce a nephrotoxic protein. The term MGRS was needed to improve the classification of these diseases for research purposes, and to accurately categorize them as pathalogical, so that government agencies could allocate the resources necessary for their treatment. The diagnosis of MGRS can be established only by performing a kidney biopsy that either demonstrates the presence of monotypic immunoglobulin deposits or infers their involvement in the case of C3 glomerulonephritis or thrombotic microangiopathy with a circulating monoclonal immunoglobulin. Clinicians will need to balance the risk of missing a diagnosis against those of the complications of renal biopsy; therefore, the judicious use of renal biopsy is important. Detection of a monoclonal immunoglobulin, in addition to helping to establish the diagnosis of MGRS, has diagnostic and prognostic value and is also used to predict treatment responses. Haematological evaluation might require peripheral blood flow cytometry, bone marrow biopsy and imaging studies to assess localized disease.

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