

# Monoclonal gammopathy of clinical significance (MGCS): when monoclonal gammopathy of undetermined significance (MGUS) is no longer undetermined

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## Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is a condition characterized by the presence of a monoclonal immunoglobulin (mIg) without its organ- or tissue-damaging effect. In recent years, attention has been paid to patients who show a MGUS-like condition, but at the same time present damage to the kidneys, peripheral nerves, or skin, resulting from the deposit of mIg. These disorders do not meet the criteria for smoldering myeloma or multiple myeloma. In 2018, the term ‘monoclonal gammopathy of clinical significance’ (MGCS) was introduced for this group of patients. The dysfunction associated with MGCS is the result of the toxic activity of a monoclonal protein produced by dangerous, small clones of B cells and plasmocytes. Taking this into account, the term ‘MGUS’ should be limited to those cases where no association with mIg organ or tissue damage can be demonstrated, whereas the term ‘MGCS’ (monoclonal gammopathy of clinical significance) should be used in patients in whom the monoclonal protein plays a direct role in damage, especially to the kidneys, skin, and nervous system. This article summarizes the current state of knowledge of the main syndromes and symptoms of MGCS.

**Key words:** monoclonal gammopathy of undetermined significance (MGUS), monoclonal gammopathy of clinical significance (MGCS), monoclonal gammopathy of renal significance (MGRS), neurological MGCS, cutaneous MGCS

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## Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a condition characterized by the presence of a monoclonal gammopathy (MG), but without end organ damage [1]. The diagnosis of MGUS requires the serum monoclonal (M) protein and bone marrow plasma cells to be below 3.0 g/dL and 10%, respectively. As MGUS progresses to multiple myeloma (MM) or Waldenström’s macroglobulinemia slowly, treatment is not usually initiated until the diagnosis of these malignant conditions. At the beginning of this century, researchers’ attention was drawn

to the increasing variety of pathological kidney conditions in patients with MGUS. As these patients did not meet the criteria for multiple myeloma (MM) or even smoldering myeloma (SMM), they were misdiagnosed as MGUS with coexisting renal disorder, for example “glomerulonephritis with MGUS” [2]. Unfortunately, MGUS was misrepresented in this context, as monoclonal gammopathy did not in fact have ‘undetermined significance’ in these patients. Despite their nonmalignant nature, these diseases were associated with high morbidity and mortality [3]. Therefore, in 2012 the term “monoclonal gammopathy of renal significance” (MGRS) was introduced in order to distinguish the

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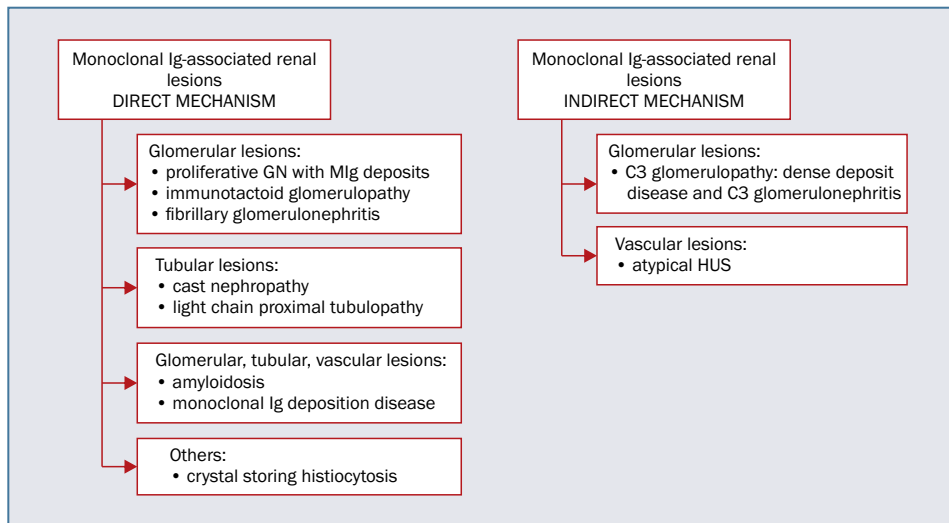
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**Figure 1.** Renal lesions associated with monoclonal gammopathy of renal significance (MGRS) according to ultrastructural characteristics of deposits in kidney (acc. to [9])

nephropathic nature of these diseases from the truly benign monoclonal gammopathy of undetermined significance.

The goal was to segregate patients with MGUS, who have no evidence of end-organ damage (and a relatively good prognosis), from those with MGRS, who are at risk of developing progressive kidney disease (with a possibly fatal outcome) [4].

It became increasingly apparent that another term was required for patients with a small clone of B-cells producing monoclonal proteins that caused serious, potentially life-threatening disease. In 2018, the term “monoclonal gammopathy of clinical significance” (MGCS) was introduced. MGCS is a monoclonal gammopathy characterized by two main features: a quiescent underlying clone and symptoms associated with the monoclonal immunoglobulin [5]. MGCSs can be divided according to the different systems affected, the most common of which are the kidneys, nervous system, and skin. It must be emphasized however that there is an overlap in some cases, due to a systemic, multiorgan presentation and disease course.

### Monoclonal gammopathy of renal significance (MGRS)

Monoclonal gammopathy of renal significance (MGRS) is a group of disorders in which a monoclonal immunoglobulin secreted by a nonmalignant or premalignant B cell or plasma cell clone causes renal damage [4]. These disorders do not meet the diagnostic criteria for overt, symptomatic MM or other lymphoproliferative diseases. It must be underscored that MGRS can also be associated with other hematological disorders, such as SMM, smoldering Waldenström’s macroglobulinemia, and monoclonal B cell lymphocytosis (MB) [6–8].

The renal lesions in MGRS are primarily due to the abnormal deposition or activity of monoclonal proteins (light chains, heavy chains, or intact immunoglobulins) within the kidneys, specifically within the glomeruli, tubules, vessels, and interstitium that depends on the specific biochemical characteristics of the involved pathogenic protein.

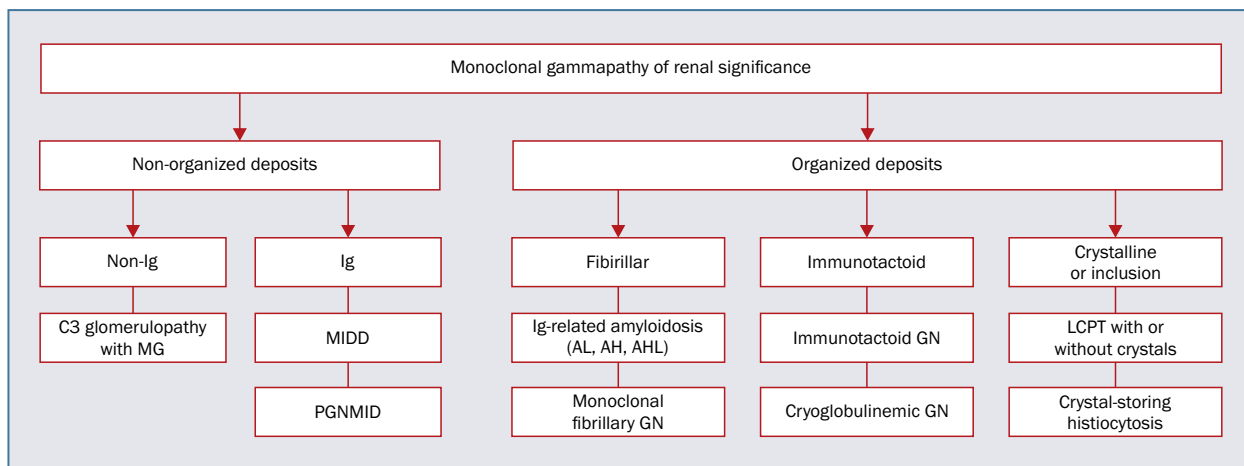
Renal lesions that are associated with MGRS can be categorized according to the ultrastructural characteristics of the deposits in the kidney, if present (Figure 1) [9]. These deposits are divided into organized (with substructure) and nonorganized (without substructure, granular). In some cases of MGRS, including thrombotic microangiopathy associated with monoclonal gammopathy (i.e. in POEMS syndrome [polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes]), deposits within the kidney are not visible [10].

The mechanism of renal injury in MGRS can be direct with the deposition of the mIg, but in a few cases the mechanism is indirect, with renal lesions as the result of dysregulation of the complement pathway by the mIg (Figure 2) [11].

### Clinical manifestation and diagnosis

A diagnosis of MGRS should be suspected in the following:

1. Patients with a nonmalignant or premalignant monoclonal gammopathy [e.g. MGUS, SMM, smoldering Waldenström’s macroglobulinemia, or monoclonal B cell lymphocytosis (MBL)] who present with unexplained renal impairment and/or proteinuria.
2. Patients who present with unexplained renal impairment and/or proteinuria, and in whom during the evaluation of renal disease are found to have a monoclonal



**Figure 2.** Renal lesions associated with monoclonal gammopathy of renal significance (MGRS) according to mechanisms of renal injury (acc. to [11])

gammopathy e.g. by serum or urine protein electrophoresis or immunofixation or by serum free light chain assay. Urine free light chain assay does not have any known diagnostic value with regard to these disorders.

A kidney biopsy must be performed in patients suspected of having MGRS, unless contraindicated. The presence of monoclonal immunoglobulin deposits in the kidney confirms the diagnosis of MGRS. For unknown reasons, a large majority (70–80%) of patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) do not have a detectable circulating monoclonal gammopathy, both by serum and by urine monoclonal protein testing. Moreover, plasma cell or B cell clones on bone marrow aspirate and biopsy are not detectable. The monoclonal protein is only found in the kidney in patients with PGNMID, therefore the diagnosis of MGRS in these patients is usually established following kidney biopsy for the evaluation of unexplained renal insufficiency and/or proteinuria or renal allograft dysfunction.

The treatment of monoclonal gammopathy-associated renal lesions aims to eliminate the underlying clone of plasma cell population in order to decrease or stop the production of the harmful M protein. The most efficient treatment is to use the chemotherapy regimens that have been developed for the treatment of multiple myeloma and AL amyloidosis.

Unfortunately, MGRS recurs frequently and rapidly after kidney transplantation, therefore achieving complete hematological remission prior to transplantation is essential [12, 13].

The treatment options according to Leung [14] are presented in Figure 3.

### Cutaneous monoclonal gammopathies of clinical significance (cutaneous MGCS)

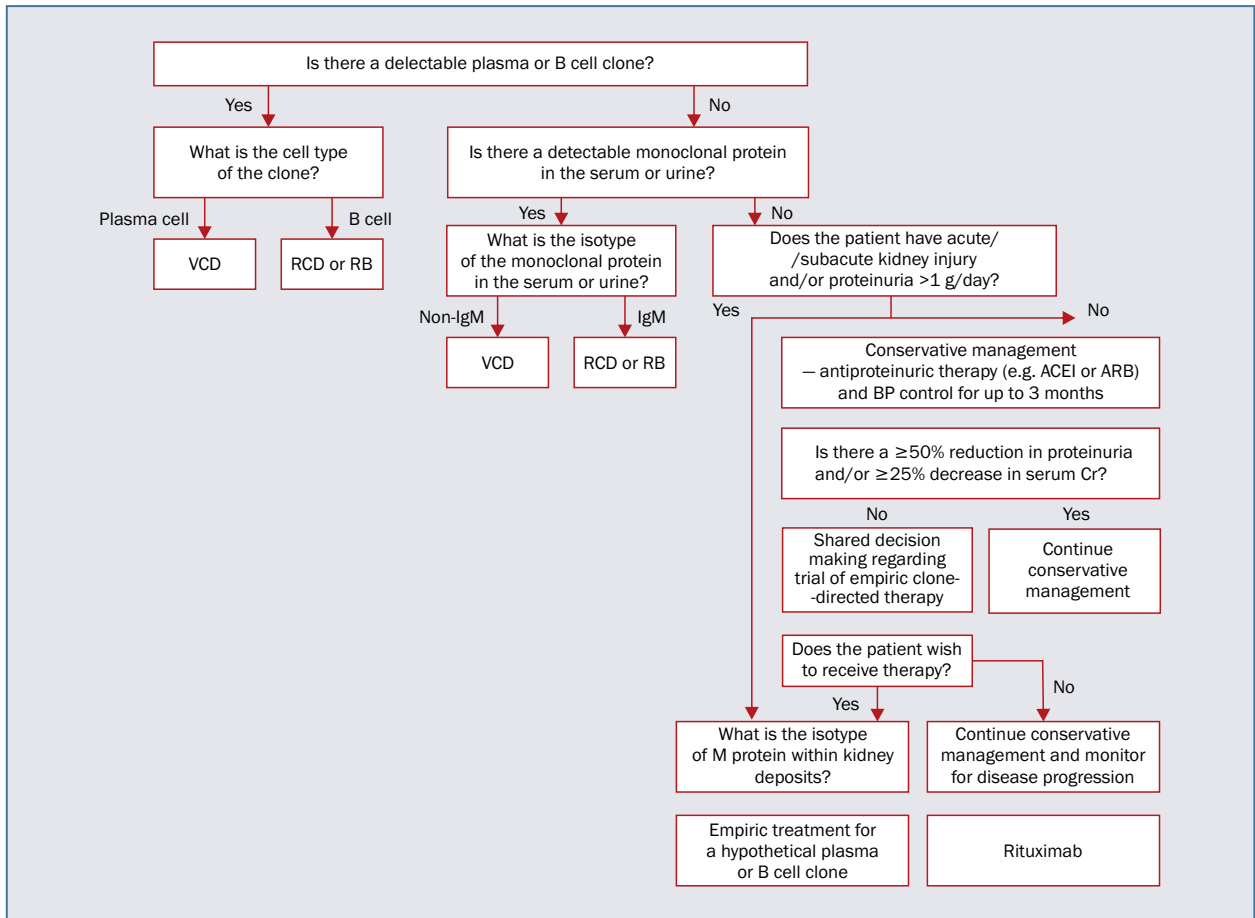
Cutaneous MGCSs include scleromyxedema, Schnitzler syndrome, necrobiotic xanthogranuloma (NXG), TEMPI

syndrome, cryoglobulinemia, and systemic capillary leak syndrome (SCLS).

Scleromyxedema is a rare systemic mucinosis characterized by generalized papular and sclerodermoid cutaneous eruptions. It is usually associated with monoclonal gammopathy involving an immunoglobulin G (mIgG) isotype with slow electrophoretic mobility [15]. Usually, scleromyxedema is a result of a small clone of secretory plasma cell (commonly referred to as MGUS) that may be associated with severe organ damage and could be a part of the MGCS [16]. Various types of extracutaneous involvement have been described in scleromyxedema, in particular neurological, gastrointestinal, cardiovascular, and joint impairments. The high mortality of scleromyxedema is primarily a result of treatment toxicity and dermatoneuro syndrome (DNS), as well as severe acute encephalopathy, usually manifested by epileptic seizures and/or coma. The efficacy of high-dose intravenous immunoglobulin (HDIViv) in the treatment of cutaneous symptoms of scleromyxedema has been described, and in 2020 Mahevas et al. presented a therapeutic algorithm for the treatment of MG-associated scleromyxedema [17, 18].

Schnitzler syndrome is another exceedingly rare, probably autoinflammatory, adult-onset disease. Since its first description in 1972, only 300 or so cases have been reported. The disease hallmark is the presence of a monoclonal IgM- $\kappa$  protein in the vast majority of reported cases (classical type), although monoclonal IgG has been identified in a minority (variant type) [19]. Clinical phenotype with a chronic urticaria-like rash and a monoclonal IgM or IgG paraprotein is obligatory. Interleukin (IL)-1 $\beta$  plays a key role in this disease. The efficacy of novel anti-IL-1 antibodies such as rilonacept and canakinumab in the treatment has been proven [20]. Careful tracking of C-reactive protein level may be helpful in the monitoring of this disease [21].

Necrobiotic xanthogranuloma (NXG) is a non-Langerhans cell histiocytosis classically associated with paraproteinemia



**Figure 3.** Algorithm of treatment of glomerulonephritis with monoclonal Ig deposits (acc. to [14])

attributable to plasma-cell dyscrasias or lymphoproliferative disorders, first described in 1980 [22]. The pathogenesis of NXG remains unclear; the paraprotein-lipoprotein interaction has been studied [23]. NXG is considered to be a skin manifestation of systemic disease. Extracutaneous involvement including the eyes, heart, gastrointestinal tract, liver, and lungs can result in organ dysfunction and death [22]. Clinically, yellow-to-orange papules, plaques, and/or nodules in a periorbital distribution are classic.

The diagnostic criteria for necrobiotic xanthogranuloma are below.

Major criteria:

1. Cutaneous papules, plaques, and/or nodules, most often yellow or orange.
2. Histopathological features demonstrating palisading granulomas with lymphoplasmacytic infiltrate and zones of necrobiosis. Characteristic features, that are variably present, include cholesterol clefts and/or giant cells (Touton or foreign body).

Minor criteria:

1. Paraproteinemia, most often IgG-k, plasma-cell dyscrasia, and/or other associated lymphoproliferative disorder.

## 2. Periorbital distribution of cutaneous lesions.

Both of the major criteria, and at least one minor criterion, are required for diagnosis, applicable only in the absence of foreign body, infection, or other identifiable cause [24]. In a multicenter cohort, intravenous immunoglobulin had the best response rate (100%), followed by antimalarial drugs (80%), intralesional triamcinolone (75%), surgery (75%), chemotherapy (67%), and lenalidomide or thalidomide (63%) [25].

TEMPI syndrome is a rare and acquired disorder characterized by five features: telangiectasias; elevated erythropoietin and erythrocytosis; monoclonal gammopathy; perinephric fluid collections; and intrapulmonary shunting [26]. TEMPI syndrome generally manifests in the fourth or fifth decade of life, in both men and women, and without any discernable ethnic or geographical predisposition. Patients firstly present with erythrocytosis and telangiectasias, and many have been erroneously diagnosed with polycythemia vera and initiated on programs of therapeutic phlebotomy. In all patients, laboratory values are notable for an elevated serum erythropoietin and the lack of a JAK2 mutation. In those patients who have been tested, hemoglobin electrophoresis and hemoglobin oxygen affinity testing have been

normal. Telangiectasias are seen most prominently on the face, upper back and chest. The hands are also commonly affected, whereas the lower extremities seem to be spared of telangiectasias. The characteristic feature of TEMPI syndrome is a monoclonal gammopathy. Serum erythropoietin measurements can be extremely high: >5,000 mIU/mL (normal range 3–19 mIU/mL), driving a predictable abnormalities syndrome in which the monoclonal antibody is almost always restricted [10].

The diagnostic criteria for TEMPI syndrome are:

I. Major criteria:

1. Telangiectasis.
2. Elevated erythropoietin and erythrocytosis.
3. Monoclonal gammopathy.

II. Minor criteria:

1. Perinephric fluid.
2. Intrapulmonary shunting.

Other: venous thrombosis.

Complete resolution of symptoms following treatment with plasma cell-directed therapy supports the hypothesis that the monoclonal antibody is causal and pathogenic [26].

Neutrophilic dermatoses associated with monoclonal gammopathy refer to a group of cutaneous inflammatory disorders characterized by neutrophilic infiltration of the skin. This has been reported in association with various conditions including autoimmune diseases, inflammatory bowel diseases, myeloproliferative disorders, and (most frequently) monoclonal gammopathy [27]. Analysis has revealed that patients with neutrophilic dermatoses share a particular cytokinic pattern, with increased rate of IL-6, vascular endothelial growth factor, intercellular adhesion molecule-1, and granulocyte colony-stimulating factor (G-CSF), but not granulocyte-macrophage colony-stimulating factor (GM-CSF).

The data highlights a strong association between IgA isotype and neutrophilic dermatoses, and the existence of a specific inflammatory profile of cytokine. Although neutrophilic dermatoses do not appear to be directly related to the mIg, and can be treated by anti-inflammatory or immunosuppressive drugs, in the era of new antimyeloma drugs the role of plasma cells and neutrophil function should be further investigated.

Idiopathic systemic capillary leak syndrome (SCLS; Clarkson's disease), is characterized by a capillary leak resulting in sudden-onset shock and anasarca caused by plasma extravasation (up to 70% of total plasma volume). The diagnostic triad is composed of the so-called 'three Hs' which occur in the absence of secondary causes of these findings: hypotension, hemoconcentration, and hypoalbuminemia. Sixty eight percent of adult patients with SCLS have monoclonal proteins, most commonly IgG-k. The differential diagnosis for an acute attack includes sepsis, anaphylaxis, and hereditary angioedema. Treatment at the time of an acute attack is supportive, with

fluid resuscitation until flare subsides, which typically occurs over the course of a few days. Empiric prophylaxis with IVIG is recommended [28].

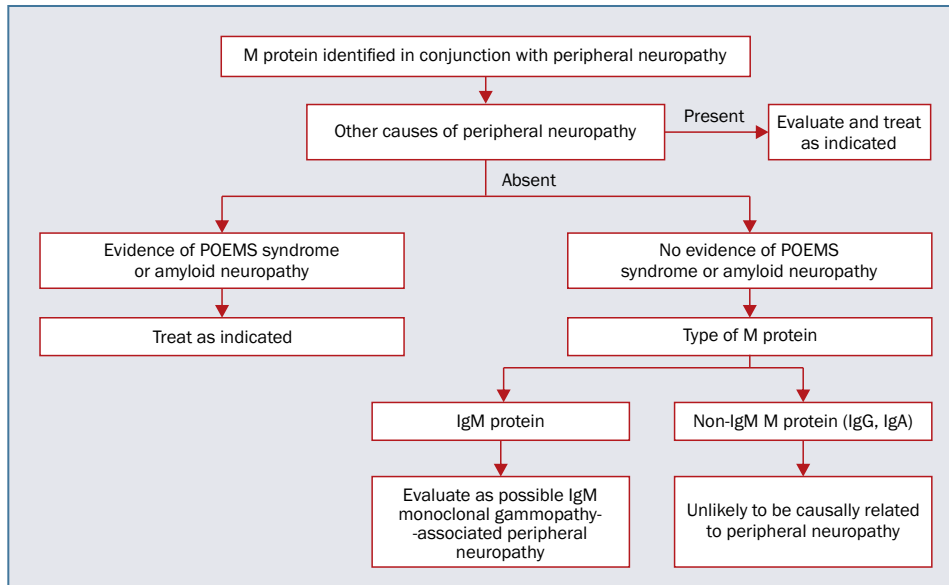
## Monoclonal gammopathy keratopathy

Corneal and conjunctival immunoglobulin deposition is rare, and its discovery is nearly always indicative of a systemic paraproteinemia. In 2005, Garibaldi et al. [29] noted ultrastructural structure similarity and a comparable to immunotactoid glomerulopathy. They coined the term 'immunotactoid keratopathy'. Immunoproteinemia has been found to be present in 98% of reported corneal cases; it was monoclonal in 57% of cases and associated with plasma cell myeloma in the other 43% [29]. Early recognition of corneal immunoglobulin deposition in patients without a known history of paraproteinemia is essential. The optimal management of corneal immunoglobulin deposition is controversial. According to the experience of Milman and several case reports, a more aggressive systemic intervention can modify corneal findings favorably and may improve visual status, but as yet the data remains scant and inconclusive [30].

## Neurological MGCS

Neurological MGCS includes light-chain amyloidosis (AL), POEMS syndrome, cryoglobulinemia, CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, M-protein, cold agglutinins and disialosylated antibodies), and DADS-neuropathy-distal demyelinating neuropathy formerly known as "MGUS-related peripheral neuropathy". It is important to distinguish peripheral neuropathy associated with monoclonal gammopathy from two other well-known diseases with specific criteria of diagnosis, i.e. immunoglobulin light chain (AL) amyloidosis, and neuropathy associated with osteosclerotic myeloma (POEMS syndrome) [31]. In both AL amyloid neuropathy and POEMS, the link between the neurological process and the M protein is well documented, and therapy is targeted at the underlying condition [32]. Peripheral neuropathy is more frequently observed with monoclonal IgM proteins than with IgG or IgA M proteins [32]. There are some differences in the clinical presentation of neuropathic IgM M proteins compared to IgG or IgA M proteins [33].

Overall, peripheral neuropathy associated with monoclonal IgM gammopathy presents itself as distal, acquired, demyelinating, symmetric M-protein neuropathy (DADS-M) [34]. It is usually diagnosed in males between the ages of six and nine as a distal symmetrical neuropathy causing sensory ataxia due to affection of large fibers of the sensory nerves. Motor involvement can occur, but is usually mild and distal, and cranial nerve involvement is rare. Anti-MAG antibodies are present in approximately



**Figure 4.** Algorithm for evaluation of patients with a monoclonal immunoglobulin with peripheral neuropathy (acc. to [31])

50% of patients; however, there is no difference in the severity or type of neuropathy with or without anti-MAG antibodies. Treatment includes immunoglobulin IV (IVIg) and rituximab [35].

Monoclonal proteins other than IgM can be observed in the full spectrum of neuropathic phenotypes, from the more common length-dependent axonal sensorimotor neuropathy, to chronic inflammatory demyelinating polyneuropathy (CIPD), which is mainly motor with proximal and distal involvement [36]. A Mayo Clinic study of 65 MGUS patients with peripheral neuropathy showed no significant clinical differences between IgG MGUS and IgA MGUS patients. Patients with IgG MGUS may have antibodies to nerve antigens, even in the absence of clinical neuropathy. Moreover, in CIPD, patients with and without paraprotein respond similarly to treatment.

An algorithm devised by Chaudhry for the evaluation of patients with a monoclonal protein identified in conjunction with peripheral neuropathy is presented in Figure 4 [31].

## Summary

MGCSs are a constellation of diseases associated with clonal, nonmalignant B cells or plasma cells that produce monoclonal proteins and a pathology through diverse, ill-defined mechanisms.

The organs most affected among patients with MGCS are the kidneys, nerves, and skin. Some MGCSs predominantly involve only one organ, while others are systemic diseases that alter multiple organs. Diagnoses and assessment of the severity of the symptoms must be considered in order to institute the appropriate therapy.

The term 'MGUS' should be limited to cases where an association with end-organ damage cannot be demonstrated. Meanwhile, the term 'MGCS' should be used when the monoclonal protein plays a direct role in the pathomechanism of the kidneys, skin or central nervous system disorder.

Hopefully, this distinction will alert physicians to the seriousness of these conditions, and clarify the role of chemotherapy.

## Author's contributions

LU-Z – sole author.

## Conflict of interest

None.

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None.

## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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