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– CASE REPORTS –

A Rare Case of Immunotactoid Glomerulopathy Associated with Monoclonal Gammopathy of Renal Significance and Potential Multiorgan Involvement

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Abstract

The term MGRS (Monoclonal Gammopathy of Renal Significance) is a newly recognized entity characterized by the renal deposition of a monoclonal protein. It arises in the context of hematologic disorders that do not meet the diagnostic criteria for plasma cell dyscrasias or lymphoma. Numerous disease entities fall under the MGRS category, each associated with a specific type of monoclonal protein that causes renal injury. This category also includes Immunotactoid Glomerulopathy (ITG), a rare glomerular disorder identified by the existence of immunoglobulin deposits in the glomeruli. These deposits have a substructural arrangement resembling microtubules with diameters ranging from 15 to 50 nm with a hollow center and organized in parallel arrays.

Patients diagnosed with MGRS should undergo treatment targeting the clone producing the nephrotoxic monoclonal immunoglobulin. This is essential in preventing renal failure, as well as the progression to more advanced monoclonal gammopathies.

We present the case of a 49-year-old female diagnosed with ITG associated with monoclonal gammopathy. The condition followed an indolent course for approximately 8 years before the diagnosis. At the time of presentation to the hematologist, she also exhibited a macular skin eruption and peripheral nerve impairment

Except for the renal biopsy, other biopsies were not performed. However, during treatment and post-treatment, we observed an improvement and even the disappearance of cutaneous lesions, as well as a clinical improvement in neurological symptoms. These observations suggest a potential multiorgan involvement in the context of monoclonal gammopathy.

Keywords: *Imunotactoid Glomerulopathy; Monoclonal Gammopathy of Renal Significance*

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Introduction

In 1978, Dr. Robert Kyle described the term " monoclonal gammopathy of undetermined significance" [1] This premalignant condition is marked by the presence of a serum monoclonal immunoglobulin <30 g/l and <10% monoclonal bone marrow plasma cells, with no associated

end-organ damage attributable to the monoclonal immunoglobulin [1,2]

In 2012, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) introduced the term "monoclonal gammopathy of renal significance" (MGRS) [3][4]. This term is used to characterize a range of kidney diseases caused by the M-protein secreted by a small B-cell, lymphoplasmacytic, or plasma cell clone that does not fulfill the current hematologic criteria for specific therapy [1,5–7]

The spectrum of kidney diseases associated with monoclonal gammopathy is diverse, and the list is continuously expanding [3,5]. In MGRS, renal deposits can be categorized into organized deposits, non-organized deposits, and non-immunoglobulin deposits [1]. Additionally, these lesions can be categorized based on their localization, including glomerular, tubulointerstitial, and vascular patterns of injury, either separately or in combination [5,6]

In MGRS, renal injury occurs through a direct pathogenic mechanism involving the deposition of monoclonal immunoglobulin in various renal structures. Furthermore, there are indirect mechanisms in which the monoclonal protein acts as an autoantibody, disrupting the alternative complement pathway and contributing to additional complications[6]. MGRS can present as different types of kidney lesions [2]. Patients may experience a gradual decline in kidney function, along with indicators such as microscopic hematuria, proteinuria (ranging from mild to severe nephrotic syndrome), and proximal tubular dysfunction [5].

It is important to note that systemic presentation is frequently observed either at the time of diagnosis or as the disease advances [3]. The condition may affect different organs, including peripheral nerves, skin, and eyes. This broader clinical involvement has led to the recognition of a distinct entity known as "monoclonal gammopathy of clinical significance," a term introduced in 2018 [3].

When treating MGRS, the focus should be on quickly suppressing the toxic monoclonal immunoglobulin that damages the kidney [2]. It is highly recommended that MGRS patients be continuously monitored by a nephrologist for proteinuria, hypertension, and serum creatinine [2].

We report a case with a rare glomerular disease associated with monoclonal gammopathy. At the time of presentation to the hematologist, the patient exhibited a macular skin eruption and grade II peripheral neuropathy. After starting hematological therapy, the patient showed complete renal recovery and an improvement in neurological symptoms. The cutaneous lesions also disappeared.

Case Report

We present the case of a young 49-year-old female, with a medical history for fibrocystic mastopathy since 2010 and tuberculous lymphadenitis in 2016.

Since 2010, the patient has shown both hematuria and proteinuria during urinalysis, with a 24-hour urinary protein excretion of approximately 2-3 g/24h, but these findings were not investigated at that time.

In 2018, following routine laboratory investigations, she was diagnosed in the Hematology Department with monoclonal gammopathy of undetermined significance IgG Kappa (MGUS IgG Kappa).

Considering the persistent proteinuria and hematuria, the patient was referred to the Nephrology Department for further investigation of renal function. During the renal evaluation in July 2019, no azotemic retention syndrome was detected (creatinine = 0.67 g/dl, eGFR = 104 ml/min/1.73 m², BUN = 31 mg/dl), and the urinalysis did not reveal hematuria. The proteinuria/24 h at the time of presentation was 1.5 g/24h. Serum albumin was normal (4 g/dl), autoimmune markers (C3, C4, rheumatoid factor, ANA, ANCA, dsDNA) were within normal limits, and cryoglobulins were absent

Even though hematuria was not evident in the urinary sediment analysis at that time, there was a suspicion of potential glomerular involvement associated with monoclonal gammopathy. Additionally, in the context of the association with tuberculous lymphadenitis, the possibility of secondary amyloidosis could not be ruled out.

Therefore, to establish a precise diagnosis, the Nephrology Department opted to conduct a renal biopsy and the results indicated immunotactoid glomerulonephritis with IgG kappa deposits.

Immunofluorescence revealed granular deposits within the glomeruli that stained positive for IgG and kappa light chain, as well as positivity for C3c (Figure 1, Figure 2).

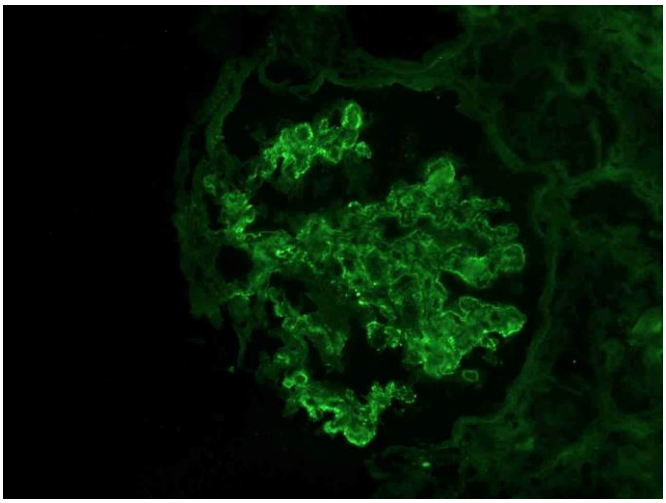

Figure 1. IgG- strongly positive granular deposits of IgG along the GBM and in the mesangiu

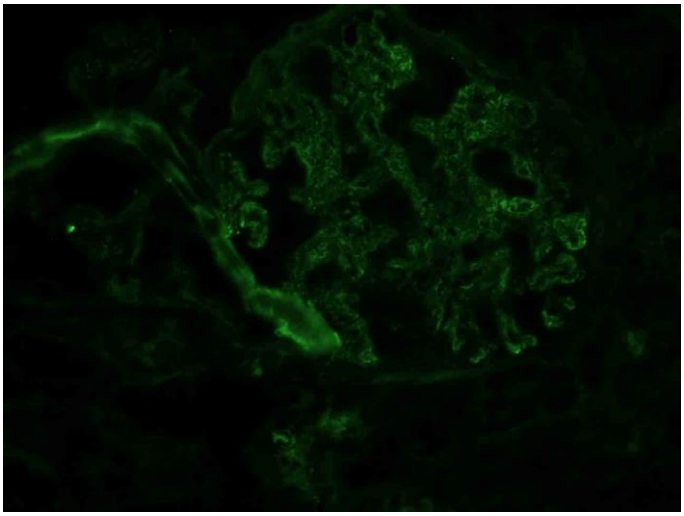

Figure 2. Kappa- less intense staining of Kappa along GBM and in the mesangiu

Electron microscopy highlighted organized deposits with a microtubular appearance, approximately 30-40 nm in diameter, with a hollow center and parallel arrays with subendothelial and mesangial locations (Figure 3, Figure 4, Figure 5).

Considering the renal histopathological aspect of immunotactoid glomerulonephritis, the patient was referred to our Hematology Department. A subsequent bone marrow aspiration revealed normocellular bone marrow with approximately 8% plasma cell involvement, FISH study for multiple myeloma was normal, showing no del17p, t(4;14), t(14;16), or t(14;16) abnormalities.

Further investigations through protein serum electrophoresis and protein serum immunofixation demonstrated the presence of an IgG kappa monoclonal protein. The Monoclonal protein spike (M-spike) was measured at 0.9 g/dL. The serum levels of immunoglobulins were as follows: IgA =1.48 g/l (reference range 0.7-4 g/l), IgG =14.8 g/l (reference range 7-16 g/l), and IgM =1.17 g/l (reference range 0.4-2.3 g/l). Serum κ and λ free light chains were 18.2 mg/L (reference range: 3.3-19.4 mg/L) and 12.7 mg/L (reference range: 5.71-26.3 mg/L) respectively, with the κ/λ free light chain ratio at 1.43 (reference range: 0.26-1.65). At the time of diagnosis, urinary protein immunofixation was negative, and repeated urinalysis revealed a small amount of hematuria (RBC = 35 /mm) and measurable proteinuria.

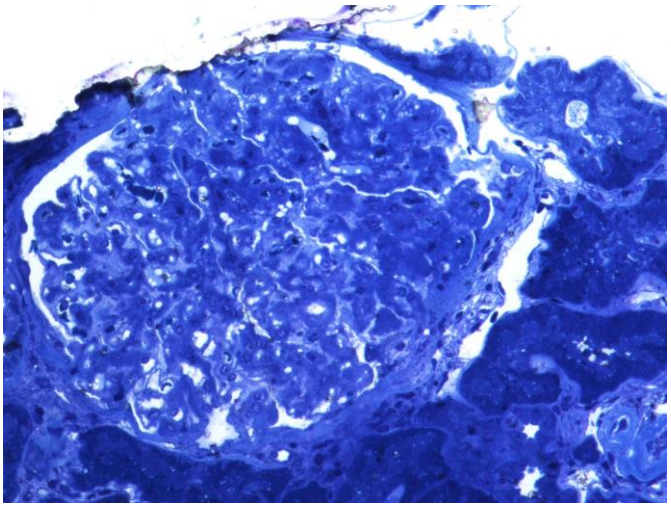

Figure 3. AT- expansion of mesangial areas with focal hypercellularity and irregular thickening of the capillary walls.

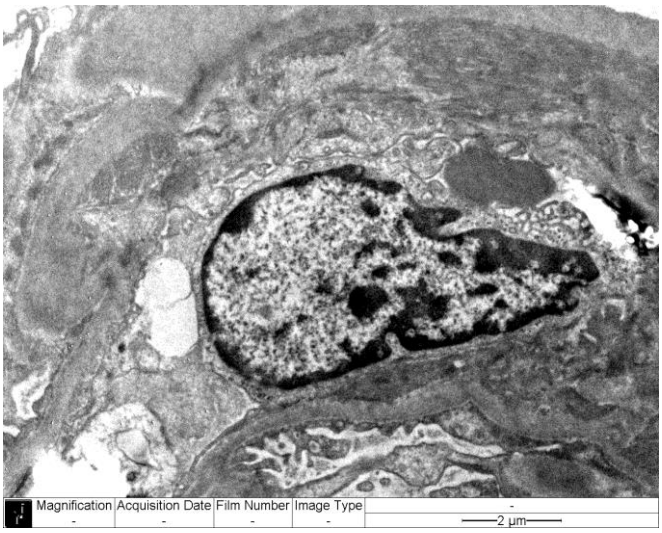

Figure 4. ME1- subendothelial deposits with microtubular ultrastructure organized in parallel arrays

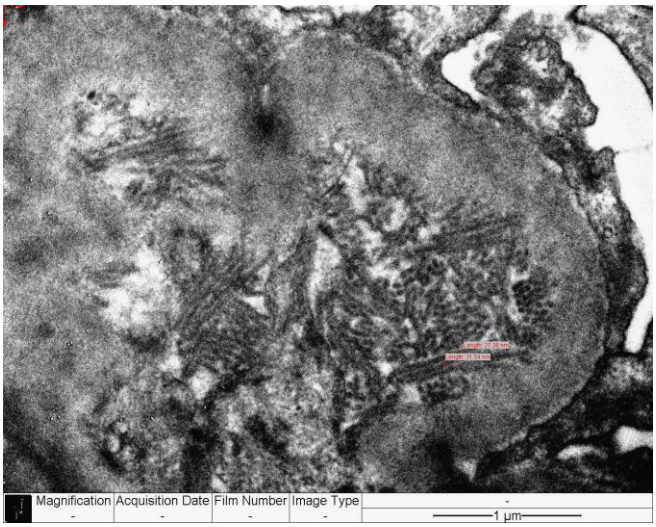

Figure 5. ME 2- mesangial deposits with microtubular ultrastructure organized in parallel arrays, with 30 nm in diameter

Whole body CT scan did not reveal osteolytic lesions.
During the clinical examination, there were no signs of peripheral edema or high blood pressure observed in the patient. However, a macular skin eruption was noted on the cervical and anterior thoracic areas, appearing around 2 years ago but not investigated at that time.
Upon admission, the patient described persistent paresthesia in the lower limbs. This led to an electromyography (EMG) which revealed the presence of a moderate sensory polyneuropathy in the lower limbs and a mild right carpal tunnel syndrome with strictly sensory impairment.
These findings, coupled with the patient's cutaneous involvement, raised concerns about the possibility of a systemic pattern of involvement.
The final diagnosis was Monoclonal Gammopathy of Clinical Significance: renal (immunotactoid glomerulonephritis) and neurological (grade 2 sensory polyneuropathy) involvement along with potential cutaneous involvement
We initiated CyBorD-type induction treatment (a total of 6 cycles) with weekly administration of Cyclophosphamide, Bortezomib, and Dexamethasone. Weekly administrations were preferred to avoid neurologic toxicity associated with Bortezomib. However, after the first cycle of therapy, the patient experienced a worsening of paresthesia in the lower limbs, leading to a reduction in the Bortezomib dose to -1 (1 mg/m^2)
Additionally, considering the young age, the patient was proposed for autologous stem cell transplantation, but due to external factors such as the epidemiological situation (COVID-19), it could not be performed.
After 4 cycles of treatment, a hematological partial response was achieved (reduction of M spike by 78%) with normal K/L ratio. Following the hematologic response, a renal response was noticed as well, with proteinuria/24 h decreasing to 0.1 g/24h and no hematuria. Neurological symptoms also improved, with a grade 2 to grade 1 polyneuropathy transition. The patient's skin condition showed significant improvement during the treatment, and by the end of the treatment, it had completely disappeared. This could indicate that the monoclonal protein was involved in the pre-existing skin condition, even though a skin biopsy could not be performed.
After completing the six treatment cycles, the patient continued to be monitored by hematological, nephrological, and neurological specialists.
Four years after the diagnosis, the renal function continues to be within the normal range, and routine urine examinations show no evidence of proteinuria or hematuria. It's important to note that, despite these positive renal outcomes, the patient has not achieved a hematological complete response (CR). Still, the reduction of the toxic monoclonal immunoglobulin contributed to achieving a favorable renal response. Regular follow-up and comprehensive monitoring remain essential in managing the patient's health and addressing potential future developments.

Discussions

MGRS has been estimated at 10% of cases of MGUS, with a prevalence of 0.32% and 0.53% in people older than 50 years and 70 years, respectively [7,8]. MGRS had a significantly higher risk of progressing to Multiple Myeloma than MGUS. Risk for progression within the first year after diagnosis was 1% in the MGUS group and 10% among MGRS patients with a median time to progression of 23 years for MGUS and 18.8 years for MGRS patients [2].
Immunotactoid glomerulopathy (ITG) is a rare kidney disease caused by deposits of monoclonal immunoglobulin in the glomeruli [9]. In around two-thirds of cases of ITG, there are monoclonal immunoglobulin deposits which are closely associated with hematologic diseases such as lymphoma, monoclonal gammopathy, or Multiple Myeloma. The remaining one-third of cases of ITP are polyclonal, and they are less commonly associated with hematologic conditions [10].
Diagnosing MGRS remains challenging for hematologists, nephrologists, and renal pathologists [8]. A kidney biopsy is required to identify the histopathology linked with MGRS and assess its severity by detecting monoclonal deposits in the kidney [6]. This is accompanied by the corresponding immunoglobulin present in the serum or urine, which plays a crucial role in confirming the diagnosis[8].
In a study conducted by the Mayo Clinic on 6300 patients diagnosed with MGUS between 2013 and 2018, only 160 patients (2.5%) underwent a renal biopsy. Among these 160 patients, 64 (40%) had lesions consistent with MGRS, while 96 patients (60%) had other renal lesions unrelated to the monoclonal protein [3,11].
They demonstrate that patients with proteinuria ≥1.5 g/d, hematuria, and an elevated free light chain ratio are at a higher risk of developing monoclonal gammopathy of

renal significance (MGRS). In such cases, a kidney biopsy should be strongly considered [3,11].

To diagnose MGRS, a combination of morphological changes observed under light microscopy, immunohistochemistry studies (either immunofluorescence or immunoperoxidase), and transmission electron microscopy is necessary [1]. Along with these, it's also important to consider the patient's medical history and laboratory findings when making a diagnosis [1].

A comprehensive hematologic study should be performed that should include protein electrophoresis with immunofixation of serum and urine samples, serum free light-chain assay, and clonal identification by bone marrow biopsy and aspiration or flow cytometry [1].

It's important to note that a systemic and multiorgan presentation is frequently common either at the time of diagnosis or as the disease progresses[3].

Conclusion

In the presented case, suspicion of Monoclonal Gammopathy of Renal Significance (MGRS) was raised by the hematologist following urine analyses that detected persistent nephritic syndrome over approximately 8 years.

It is noteworthy that a kidney biopsy is imperative for the diagnosis of monoclonal gammopathy with renal impact. The case described above, with peripheral nerve and skin involvement, indicates that this rare type of glomerulonephritis can be associated with multiple organ impairment.

Furthermore, in the case presented above, we want to emphasize the importance of hematologic-specific treatment targeted against the clone-producing monoclonal protein to prevent disease progression.

No funding for this study

Conflicts of interest

I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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