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Case Report

The Matter of Kidney Biopsy in Monoclonal Gammopathy of Renal Significance: A Case Report of a New Pattern of Immunoglobulin-Storing Histiocytosis

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Keywords
Monoclonal gammopathy of renal significance · Crystal-storing histiocytosis · Immunoglobulin-storing histiocytosis · Multiple myeloma

Abstract
Monoclonal gammopathy of renal significance (MGRS) represents a group of disorders, characterized by paraproteinemia which causes renal damage. These disorders never meet the diagnostic criteria for multiple myeloma (MM) or lymphoproliferative disease. Crystal-storing histiocytosis is one of the rarest patterns of MGRS, characterized by an accumulation of light chains of crystals within histiocyte's cytoplasm, located in bone marrow or other extramedullary sites such as the kidney, cornea, or thyme. A very few cases have been described as immunoglobulin-storing histiocytosis (IgSH) without evidence of crystals. In the recent literature, only 3 cases of IgSH have been described so far, none renal. In all cases, these very peculiar histopathological patterns are associated with lymphoproliferative or plasma cellular disorders. Here, we report a very unusual IgSH pattern in a kidney biopsy, which led to prompt detection and early therapeutic intervention, in a patient with otherwise misdiagnosed MGRS.

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Introduction

Monoclonal gammopathy of renal significance (MGRS) is a group of renal disorders caused by a nephrotoxic protein secreted by a plasma cell or B-clone [1]. These clones do not meet the criteria for specific chemotherapy, but they are related to kidney lesions, with potential progression to ESRD. In the context of proteinuria with/without renal failure, early detection and classification of a monoclonal immunoglobulin are crucial for MGRS diagnosis and therapy, usually resulting in a better outcome for these patients [2]. In this context, kidney biopsy is still irreplaceable for a correct diagnosis and for early kidney-saving therapy.

One of the rarest types of MGRS is crystal-storing histiocytosis [3–5], characterized by the accumulation of light chain crystals within histiocyte's cytoplasm, located in the bone marrow [6, 7] or other extramedullary sites such as the kidney, cornea, lymph nodes, liver, spleen, gastrointestinal tract, and thyme. Few cases have also been described as immunoglobulin-storing histiocytosis (IgSH), with or without evidence of crystals, located in the bone marrow or other sites [8, 9]. Other rare kidney diseases may present with histiocytosis, such as histiocytic glomerulopathy, but are characterized by the presence of different symptoms such as macrophage activation syndrome, and all have immunofluorescence microscopy negative for light chains [10, 11]. Here, we report a very unusual IgSH renal pattern, in a patient with wild mild renal failure and non-nephrotic proteinuria.

Case Presentation

A 70-year-old man was admitted to our hospital because of a slight increase in serum creatinine (1.6 mg/dL), with non-nephrotic proteinuria (2.7 g/24 h) and microscopic hematuria, detected on a routine check-up in January 2021. He was in good condition, with a past medical history of benign prostatic hyperplasia and juvenile idiopathic arthritis (documentation not available, no joins disfiguration at presentation). There was no history of kidney disease. Bodyweight was 70 kg (BMI 26) and normal blood pressure (120/70 mm Hg). Clinical examination, chest x-ray, and abdominal ultrasound were normal.

Laboratory tests confirmed a stage IIIa CKD (eGFR 46 mL/min/1.73 m^2), with non-nephrotic proteinuria and urinary protein/creatinine ratio of 1.64 mg/dL. Microscopic urinalysis revealed moderate dysmorphic hematuria and cylindruria. Urine culture was negative. No findings of Fanconi syndrome were found.

All autoantibodies (i.e., antinuclear, anti-double-stranded DNA, extractable nuclear antigen panel, ANCA, and anti-PLA2R antibodies, cryoglobulins) were negative, and serum immunoglobulin and complement fractions (C3, C4) were in the normal range. Viral markers (HBV, HCV, HIV) were negative. Bence-Jones protein (BJP)-kappa was observed in urine, serum protein electrophoresis, and immunofixation revealed a monoclonal protein (IgGκ 14.2%), with serum-free light chain (FLC) ratio (K/lambda = 9.22). Hemoglobin level was 10 g/dL, with white blood cells and platelets in the normal range. No hypercalcemia was detected. Echocardiography was normal (EF 75%), and no osteolytic lesions were seen on the skeletal X-ray and total-body CT scan.

A percutaneous renal biopsy was performed and showed mild thickening of glomerular basement membranes with segmental double contours. Glomerular capillary lumina were occluded by several histiocytes/macrophages (CD68-KP1 positive) (Fig. 1a, b) with cytoplasm filled with amorphous material with the reactivity of immune deposits on special stainings (PTAH, AFOG, trichrome). Immunofluorescence performed on fresh tissue showed strong

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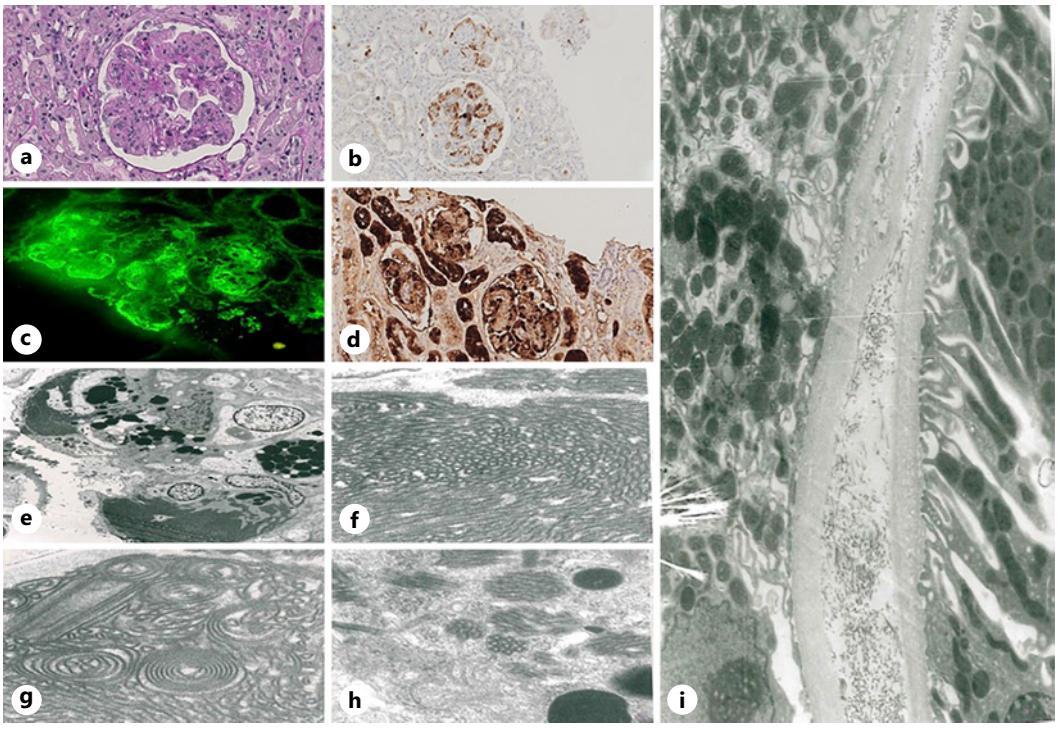

Fig. 1. Renal biopsy findings. **a** PAS staining demonstrated diffuse endocapillary hypercellularity, that was mainly constituted by histiocytes/macrophages CD68-KP1 positive; original magnification ×400. **b** Immunofluorescence on fresh tissue showed irregular, strong positivity for IgG in the cytoplasm of intracapillary glomerular histiocytes and along basement membranes; original magnification ×200. **c** Direct immunofluorescence on fresh material; original magnification ×400. **d** Immunohistochemistry performed on fixed paraffin-embedded material revealed strong glomerular positivity only for kappa light chains; original magnification ×200. **e–h** Electron microscopy demonstrated several structured electron-dense deposits with the atypical organization: some microtubular deposits with electron-lucent lumen organized in parallel arrays, some triangular or square deposits in cross-sections, others atypical structures in vortex. Original magnification ×1,900 (**e**), original magnification ×27,500 (**f**–**h**). **i** The proximal tubules did not show electron-dense deposits (original magnification ×3,810).

positivity for IgG (+++), moderate positivity for C1q (+/++), and mild staining for C3 (+), with an irregular distribution in large deposits in the cytoplasm of intracapillary glomerular mononuclear cells and granular along occasional glomerular basement membranes in a subendothelial and intramembranous location. Glomeruli demonstrated on immunofluorescence a moderate positivity for kappa chains (2+) (Fig. 1c, d) and weak staining for lambda (1+). Next, we performed immunohistochemistry on fixed paraffin-embedded material with kappa and lambda chains (with a microwave method of antigen retrieval) that revealed a strong positivity only for kappa light chains in the cytoplasm of intracapillary glomerular histiocytes, while the lambda light chains resulted substantially negative. Electron microscopy demonstrated abundant structured electron-dense deposits located in macrophages' cytoplasm and along the glomerular basement membranes, mainly in subendothelial locations or free in capillary lumens. Deposits showed various structuration: microtubules with a diameter of 50–52 nm, focally organized in parallel arrays, but on cross-sections with an unusual triangular or square shape, and other types of deposits with an atypically concentric "vortex" arrangement (Fig. 1e–h). The finding was suggestive of histiocytic glomerulopathy with an intracytoplasmic deposition of monotypic IgGk in the form of atypical organized deposits that did not belong to the entities of immunotactoid and fibrillary

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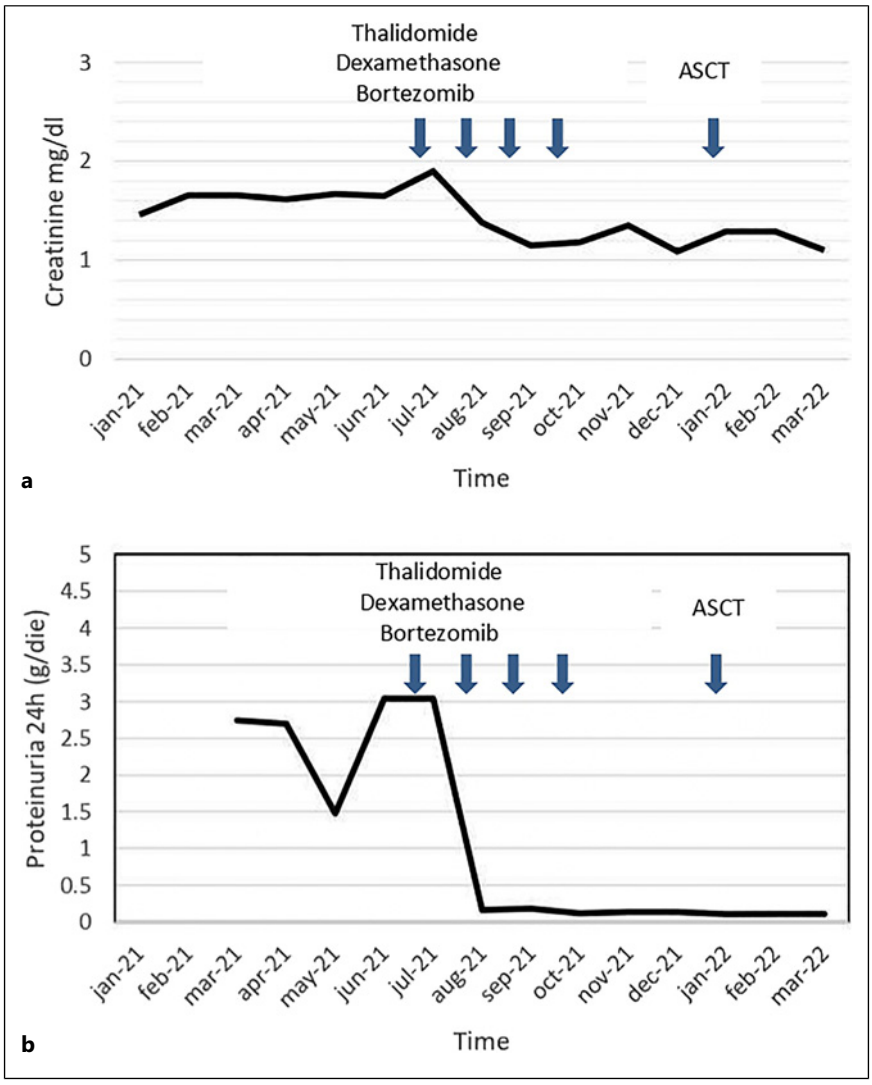

Fig. 2. Changes in renal function. **a** Changes of serum creatinine from baseline to posttreatment. **b** Changes of proteinuria from baseline to posttreatment. Chemotherapy with thalidomide, dexamethasone, and bortezomib was started in July 2021 and ASCT in December 2021. ASCT, autologous stem cell transplantation.

glomerulonephritis. The absence of cryoplugs excluded the alternative hypothesis of cryoglobulinemic glomerulonephritis.

A bone marrow biopsy was performed, showing clonal plasma cells = 30%, with IgGk restriction. Our patient started treatment with thalidomide, dexamethasone, and bortezomib, and a very good partial remission (VGPR) was achieved after four cycles, with an improvement in renal function (eGFR 60 mL/min) and a reduction of monoclonal protein (0.9%) and FLC ratio (1.74). Subsequently, he underwent autologous stem cell transplantation without complications. Three months later, he started lenalidomide for maintenance therapy. Last laboratory tests (March 2022) (Fig. 2a, b) confirm stable renal function, with normal proteinuria (0.11 g/24 h), undetectable BJP, and decreasing serum monoclonal protein (=0.6%) and FLC ratio (=1.3). Our patient is still in good condition.

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Discussion

The MGRS encompasses a variety of histopathological patterns affecting the kidney, some of them with specific peculiarities, but all with potential progression to ESRD, typically without fulfilling the hematological criteria for starting chemotherapy. Ten years ago, the term MGRS was introduced to distinguish these monoclonal gammopathies from MGUS (which cannot be associated with any end-organ damage), and from malignant conditions like symptomatic multiple myeloma (MM) or B-cell lymphoma. Since then, many renal patterns have been described so far, even if some of them remain extremely rare, such as IgSH. IgSH has been linked to crystal-storing histiocytosis, which is a rare entity characterized by the accumulation of crystallized material within histiocytes [8]. IgSH can be found in a wide range of organs/tissue sites and is divided into generalized and localized forms. A total of 140 cases were identified by a recent review, between 1987 and 2020 [8]. At diagnosis, the median age was 60 years, with an equal sex distribution. Most patients had an underlying neoplastic B-cell disorder, often MM, MGUS, or lymphoplasmacytic lymphoma (LPL), and did not present symptoms of macrophage activation syndrome, typical of histiocytic glomerulopathy, or of thrombotic microangiopathy; typical renal lesions with the typical deposition of histiocytes [10, 11]. The main affected organ systems or tissue sites were bone, followed by the head, kidney, lung, and gastrointestinal tract. IgG was the main immunoglobulin class involved, and most cases were associated with kappa light chain expression [8].

The crystal formation remains unclear, with theories regarding overproduction or failure to degrade immunoglobulins intracellularly. It has also been hypothesized that DNA mutations in the sequence for immunoglobulins may result in resistance toward lysosomal degradation by macrophages. Sometimes immunoglobulin deposition can be negative in the interstitium and tubules [11]. Regarding IgSH without crystallization, very few cases have been reported (2 cases with MM/monoclonal gammopathy, 1 with MALT thymic lymphoma), none of them renal [8, 9]. To our knowledge, our case report is, therefore, the first to demonstrate a renal IgSH without crystals, once again leading the clinician to detect an underlying plasma cell disorder.

The singularity of this pattern may contribute to widening the range of clinical presentations of MGRS, but it also underlines, once more, the importance of a prompt diagnostic approach by kidney biopsy for such patients. Early diagnosis, especially when kidney damage is still limited, usually facilitates treatment management and results in a better outcome. MGRS is a heterogeneous, but not so rare entity, that needs a common effort of both nephrologists, pathologists, and hematologists to improve management and results in the next future. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533913).

Statement of Ethics

The results presented in this paper have not been published previously in whole or part, except in abstract form. The authors declare that written informed consent was obtained from the patient for publication of the details of his medical history and any accompanying images The study was reviewed and approved by the AOU Città della Salute e della Scienza Internal Ethical Committee (protocol study number 00157/2019). The study was conducted following the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Antonella Barreca: consulting pathologist, interpretation, and analysis of kidney biopsy. Stefania Oliva: consultant hematologist and managing the patient. Paolo Randone, Manuel Burdese, Enrico Sanna, Isabella Abbasciano, Patrizia Anania, Elena Boaglio, and Luigi Biancone provided intellectual content of critical importance to the work described and approved the final version. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have followed the regulations of our institutions concerning intellectual property.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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