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Case Report

Combined renal proximal tubulopathy and crystal storing histiocytosis in a patient with κ lightchain multiple myeloma

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Summary

Multiple myeloma accounts for 10-15% of all hematologic malignancies, and 20% of deaths related to cancers of the blood and bone marrow. Diagnosis is defined by the presence of a serum monoclonal spike (M-spike) of more than 3 g/dL or more than 10% clonal plasma cells in the bone marrow and at least one myeloma-defining event, such as hypercalcemia, anemia, bone lesions, or renal impairment. The kidney is a major target organ, and renal impairment is frequently the first manifestation of the disease. Renal damage occurs in up to 40% of patients and 10-20% will require dialysis. Monoclonal immunoglobulin light chains are the major causes of renal complications in multiple myeloma. Glomerular disease, with the deposition of monoclonal immunoglobulins or their components, includes monoclonal immunoglobulin deposition disease, AL or AH amyloidosis, type I cryoglobulinemia, proliferative glomerulonephritis with monoclonal IgG deposits, immunotactoid glomerulopathy, and fibrillary glomerulonephritis. In addition, tubulointerstitial diseases with the deposition of monoclonal immunoglobulins or their components, are constituted by light chain cast nephropathy, light chain proximal tubulopathy, and crystal-storing histiocytosis.

We report the case of a 66-year-old woman who presented with albumin-predominant moderate proteinuria and renal failure. Serum and urine immunofixation electrophoresis showed monoclonal κ light chain in both. Renal biopsy confirmed κ-restricted crystal-storing renal disease involving proximal tubular epithelial cells and crystal storing histiocytosis. Multiple myeloma with crystal storing histiocytosis was discovered in bone marrow biopsy. Thus, we present an unusual case of a myeloma patient presenting light chain proximal tubulopathy and crystal-storing histiocytosis both in the kidney and in the bone marrow.

Key words: multiple myeloma, crystal-storing histiocytosis, bone marrow biopsy, light chains glomerulopathy, renal biopsy

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Conflict of interest
The Authors declare no conflict of interest.

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Introduction

Multiple myeloma (MM) results from the clonal proliferation of plasma cells in the bone marrow andsubsequent overproduction of immunoglobulins (Igs) or immunoglobulin fragments into the serum, and in urine, including free light chains (FLCs) [1]. FLCs are low molecular-weight proteins normally produced by lymphoid tissues and 1-10 mg/day are excreted in the urine [2,3]. Patients with paraprotein-related kidney disease present with various manifestations, including light chain cast nephropathy, monoclonal Ig deposition disease, light chain amyloidosis, light chain proximal tubulopathy (LCPT), and tubule-interstitial nephritis [3-5]. A majority (approximately 70%) of pathogenic FLCs is tubulopathic, and about

one-third interacts with glomerular structures (glomerulopathic FLCs) [6,7]. Myeloma cast nephropathy (MCN), the most common Ig-related crystalline nephropathy, is characterized by crystalline precipitates of monoclonal light chain (either κ or λ) within distal tubules. On rare occasions, Igs crystallization occurs intracellularly within proximal tubular cells and in histiocytes, "crystal-storing histiocytosis" (CSH) [6-8]. LCPT is classified into crystalline or non- crystalline, based on the presence or absence of crystal structures in the cytoplasm of epithelial tubular cells [3,8]. Crystal-storing histiocytosis (CSH) is characterized by crystalline refractile eosinophilic inclusions in the cytoplasm of histiocytes. CSH involving lung, bone marrow [9], kidney [10], skin [11], ocular and periorbital areas [12] has been reported, usually with underlying lymphoplasmacytic disorders, most likely lymphoplasmacytic lymphoma or multiple myeloma.

Herein, we describe a myeloma patient presenting light chain proximal tubulopathy and crystal- storing histiocytosis both in the kidney and in the bone marrow.

Materials and methods

Light microscopy

Kidney biopsy was fixed in buffered 10% formalin and embedded in paraffin. Serial 3-mm thick sections were cut and treated with hematoxylin and eosin, Jones methenamine silver, Masson trichrome, and periodic acid-Schiff reagent. In addition, Congo red staining was performed on 5-mm thick sections. Bone marrow biopsy was fixed in buffered 10% formalin, decalcified by EDTA, dehydrated in graded alcohols, and embedded in paraffin using standard techniques. Serial 3-mm thick sections were cut. Routine hematoxylin and eosin staining, Giemsa, Gomory and Prussian blue for Fedetection were used. In addition, Congo red staining was performed on 5-mm thick sections.

Immunohistochemistry microscopy

The detection system for immunostaining is BOND Polymer Refine Detection on staining platform LEICA BOND III with 30 min at 100°C with BOND Epitope Retrievial sol. 1 for antibodies Lambda (polyclonal, Dako, 1:10^5) and CD138 (clone MI15, Dako, 1:300), 20 min for antibody Kappa (polyclonal, Dako, 1:50.000), antibody CD68R/PG-M1 (clone PG-M1, Dako, 1:500) use 30 min at 100°C with BOND Epitope Retrieval 2. The Roche's CD14 antibody (clone EPR3653) are detected on platform BenchMark ULTRA using UltraView Universal DAB Detection Kit, 64 min of antigen retrieval with Cell Conditioning 1 and incubation for 32 min.

Immunofluorescence microscopy

Samples were transported in Michel's media, washed in buffer, and frozen in a cryostat. Sections, cut at 5 mm, were rinsed in buffer and reacted with fluorescein-tagged polyclonal rabbit anti-human antibodies to IgG, IgA, IgM, C3, C4, C1q, fibrinogen, and k-, and l-light chains (all from Dako, Carpenteria, CA, USA) for 1 h, rinsed, and a coverslip applied using aqueous mounting media.

Electron microscopy

For electron microscopic examination, renal biopsy was fixed with glutaraldehyde, followed by post- fixation at 4°C in osmium tetroxide for 1 h. The sections were dehydrated by passing through a graded alcohol series, treated with aceton, and then embedded in epoxy resin. Semi-thin sections measuring 1-2 µm in thickness prepared using an ultramicrotome were stained with toluidine blue and then analyzed under a light microscope. Ultrathin sections measuring 70-80 nm in thickness placed on the grids were subjected to ultrastructural examination under a transmission electron microscope FEI TECNAI G2 SPRIT BIOTWIN c/o Virology Unit of *Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna* (IZSLER) of Brescia.

Case presentation

A 66-year-old normotensive woman was referred to our Renal Division to evaluate kidney dysfunction. At the presentation serum creatinine was 138 mmol/L (measured clearance 34 ml/min), and BUN 29 mg/dl. The patient had severe ipokalaemia (2,7 mEq/L) with a renal loss of potassium (excrete fraction 22%, urinary potassium 34 mEq/24h). Urine analysis showed absent glycosuria, proteinuria 1.95 g/24 h, red cells and granular cast at sediment examination. Serum protein electrophoresis showed a hypogammaglobulinemia (8.4%). Immune electrophoresis detected a Bence-Jones protein κ, and at serum κ and λ free light chain (κ 904 mg/dl, l 11,7 mg/dl; κ/λ ratio 77). ANA, ENA, hepatitis B and C markers, HIV antibodies, Quantiferon-TB were negative; C3 and C4 were normal, as were blood cell count and other electrolytes (calcium, phosphate, magnesium, sodium), except for potassium. Serum sodium bicarbonate was 23 mEq/L.

Percutaneous ultrasound-guided renal biopsy (Fig. 1) revealed a total of 9 glomeruli: 5 patents, withoutsignificant pathologic alterations; 4 globally sclerosed. Only one glomerulus showed macrophages with abnormal intracytoplasmic accumulation of crystals. Crystal-

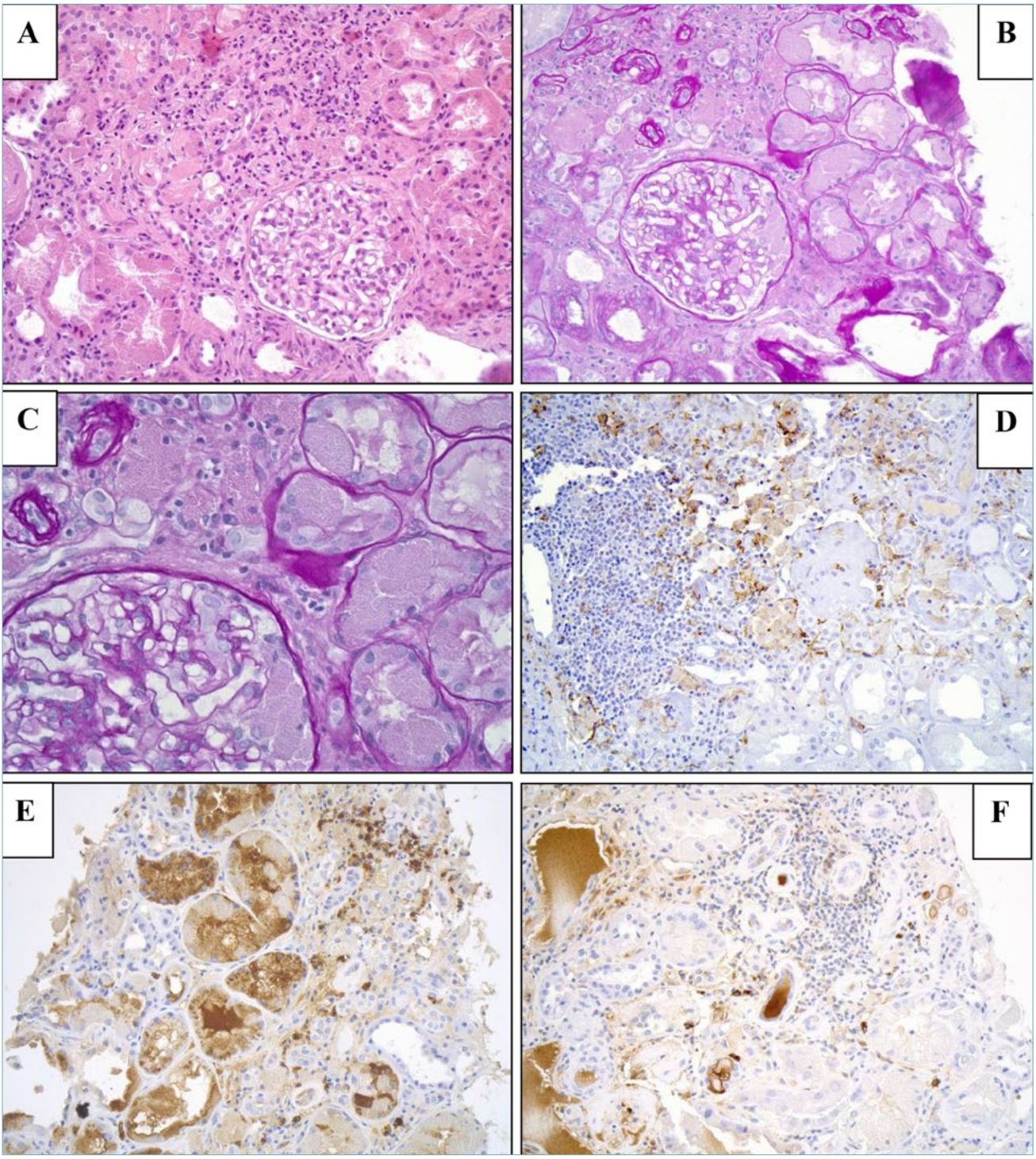

Figure 1. Renal biopsy. (A) (hematoxylin and eosin; 20x), (B) (PAS; 20x) and (C) (PAS; 40x) - Proximal tubule epithelial cells with prominent brightly eosinophilic intracytoplasmic inclusions and crystal - storing histiocytes present in the glomerulus and interstitium. (D) (immunohistochemical analyses; 20x) - Crystal-storing histiocytes were positive for CD14. (E) (immunohistochemical analyses; 20x) - κ light chain expressed in the majority of plasma cells and in the cytoplasm of proximal tubular epithelium. (F) (immunohistochemical analysis; 10x) - λ light chain expressed in rare plasma cells.

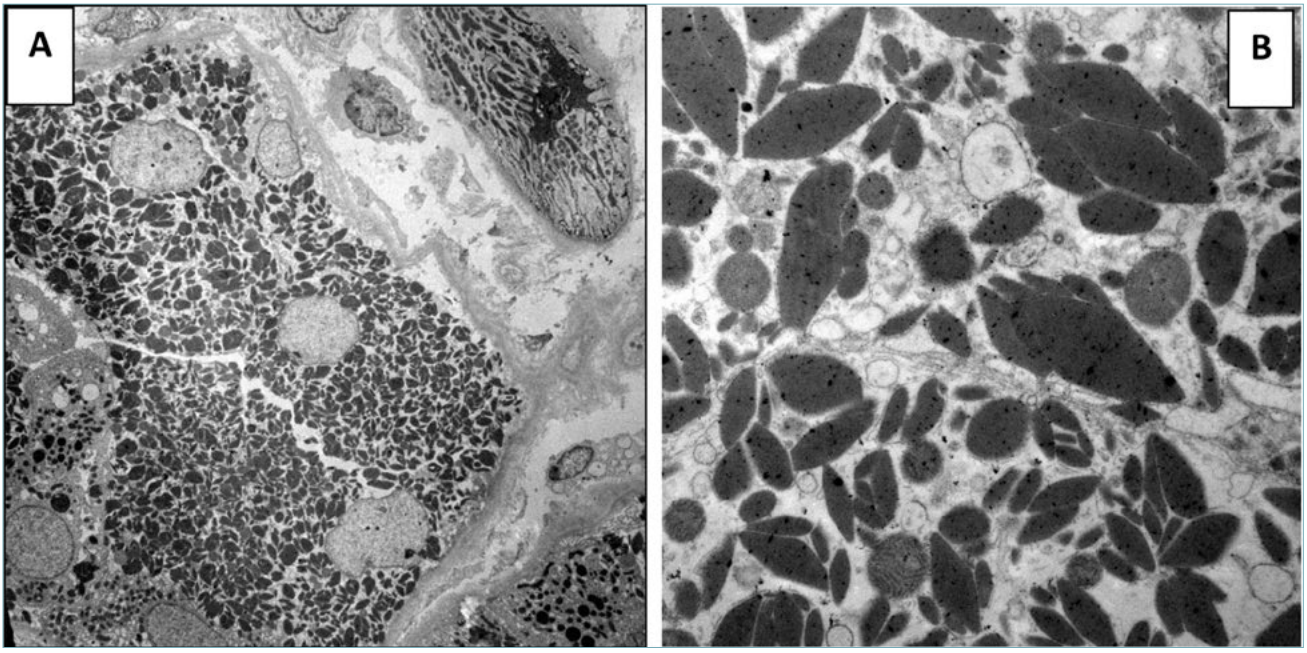

Figure 2. (A, B). Tubular epithelial cells showed intracytoplasmic electron dense, polygonal-, rhomboid- (most frequent), or needle-shaped crystalline structures.

storing histiocytes also infiltrated the interstitium. Proximal tubular epithelial cells showed prominent intracytoplasmic inclusions, some of which were sharply demarcated and rhomboid in appearance. These inclusions wereeosinophilic on the hematoxylin and eosin stain, pale on periodic acid Schiff stain. There was mild interstitial inflammation composed of mainly lymphocytes and rarer plasma cells. There were no associated with cast nephropathy or amyloid deposits. Immunohistochemical studies for κ and λ light chain on paraffin sections revealed κ monoclonal plasma cells, with variable staining of the intracytoplasmic material in tubular epithelial cells, while no staining was observed within histiocytes. Sampling for immunofluorescence consisted of 10 glomeruli and exhibited no significant glomerular positivity for IgG, IgM, IgA, C3, fibrinogen, k or λ light chains. Sampling for electron microscopy consisted of no glomeruli. Proximal tubular epithelial cells showed intracytoplasmic electron dense, polygonal-, rhomboid- (most frequent), or needle-shaped crystalline structures (Fig. 2). No electron dense deposits were observed in the tubular basal membrane.

Bone marrow biopsy (Fig. 3) showed about 10-15% of mature plasma cells infiltrate with interstitial distribution. Plasma cells showed expression of CD138, CD20, and restriction of κ light chains by immunohistochemistry. No amyloid deposits were found in the bone marrow specimen by Congo red staining, also with examination in polarized light. Moreover, bone marrow specimen showed accumulation of histiocytes, positive by CD68R/PG-M1 immunostaining. The cytoplasm ofthe histiocytes was filled with eosinophilic crystalline material that was not immunohistochemically positive for kappa light chains. There were no intracytoplasmic crystals inside plasma cells. The hematopoietic matrix was normal for cellularity and maturation. Bone marrow aspiration showed normal cellularity and maturation of hematopoietic cells, with 12% of mature plasma cells. Hemophagocytic phenomenon was not observed. Cytogenetic evaluation showed a normal female karyotype. FISH analysis excluded the presence of IgH rearrangement (14q32.33) or the presence ofdel(17p)(p13.1).

The laboratory examination revealed normal blood counts; total circulating proteins were 6.8 g/dL. No monoclonal component was found, but hypo-gammaglobulinemia was detected. Free circulating light chain were 1030 mg/L (kappa) and 11 mg/L (lambda) with a ratio of 84. Urinary light chain kappa was 5600 mg/24h. Plasmatic calcium was normal. A low dose total body CT scan excluded skeletal lithic lesions.

The diagnosis was consistent with micro-molecular kappa type multiple myeloma. The International Staging System 13 score was II. The presence of renal impairment was a sufficient criterion to start treatment.

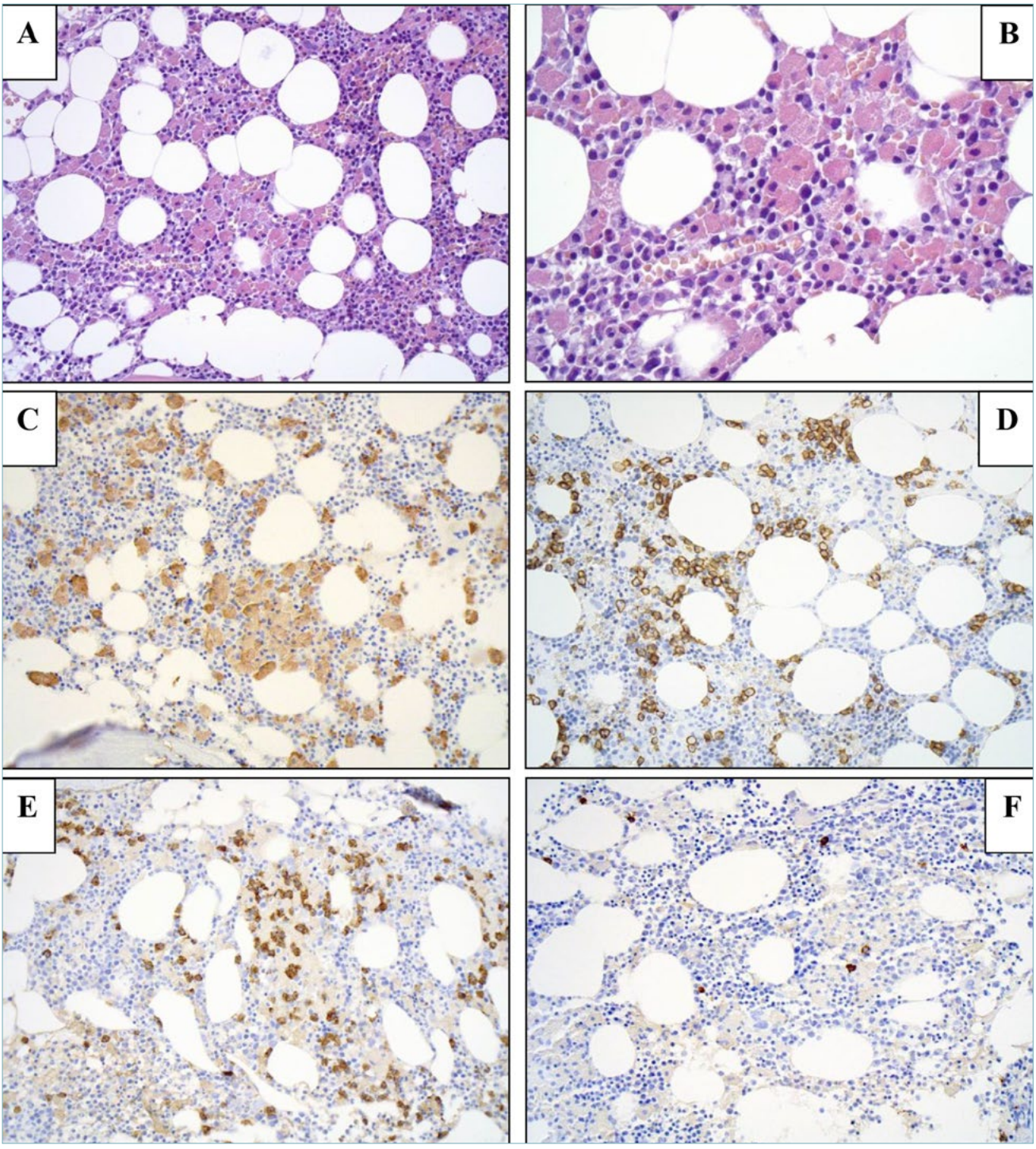

Figure 3. First bone marrow biopsy. (A) (hematoxylin and eosin; 10x) - Normocellular hematopoietic matrix with crystal-storing histiocytes. (B) (hematoxylin and eosin; 20x) - Hematopoietic matrix with crystal-storing histiocytes. (C) (immunohistochemical analysis; 10x) - Diffuse expression of CD68R by macrophages. (D) (immunohistochemical analysis; 10x) - Diffuse expression of CD138 by plasma cells. (E) (immunohistochemical analysis; 10x) - κ light chain expressed in the majority of plasma cells. (F) (immunohistochemical analysis; 10x) - λ light chain expressed in rare plasma cells.

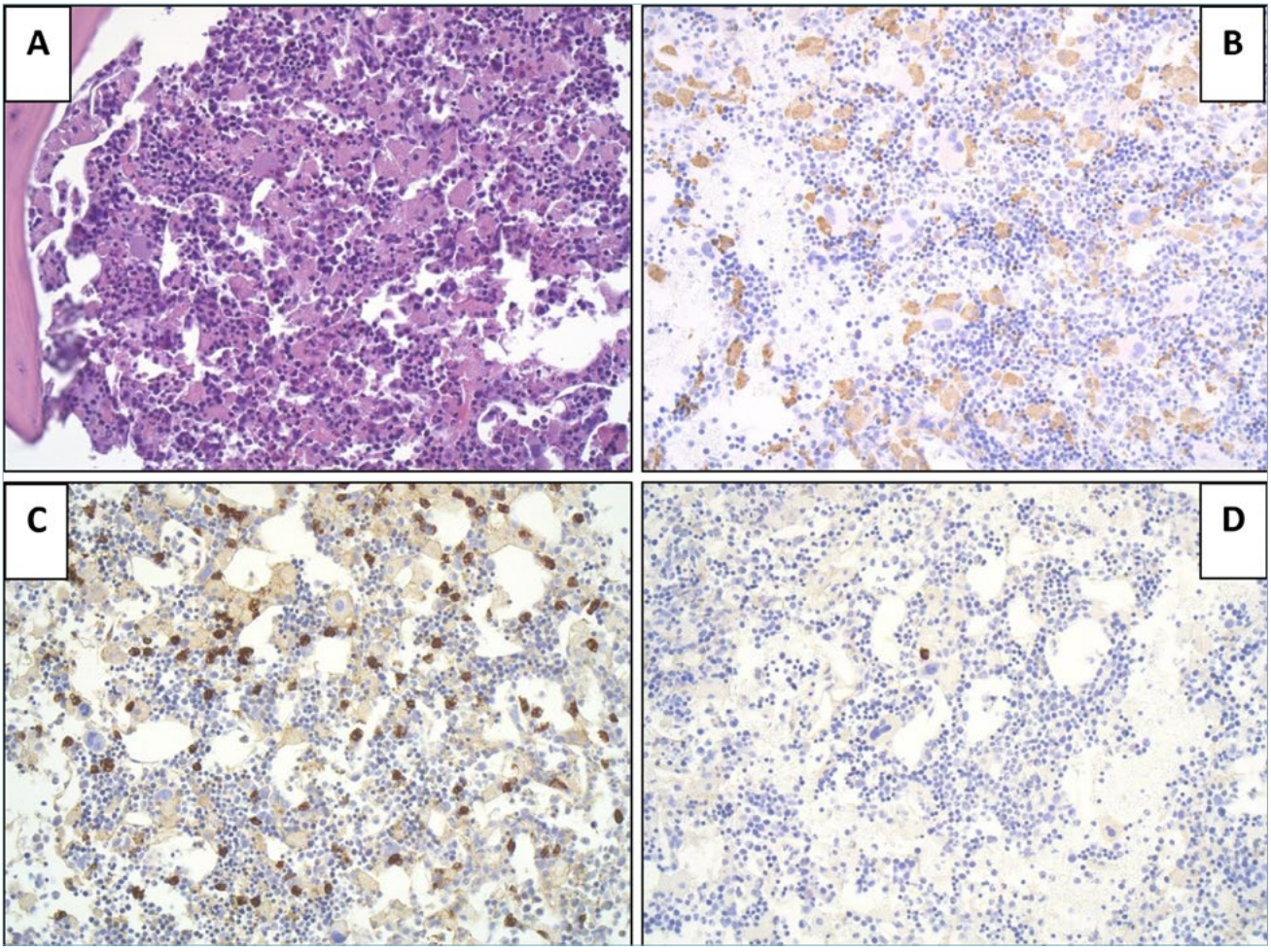

Figure 4. Second bone marrow biopsy. (A) (hematoxylin and eosin; 10x) - Light hypercellular matrix with scattered crystal-storing histiocytes. (B) (immunohistochemical analysis; 10x) - Diffuse expression of CD68R by crystal storing histiocytes. (C) (immunohistochemical analysis; 10x) - κ light chain expressed in the majority of plasma cells. (D) (immunohistochemical analysis; 10x) - λ light chain expressed in rare plasma cells.

The patient underwent induction therapy with VTD (bortezomib - thalidomide - dexamethasone) triplet. Creatinine levels immediately before treatment were 1.9 mg/dL. After 4 cycles, the kappa/lambda free light chain ratio was 29, and urinary light chain kappawas 1536/24h. A new bone marrow biopsy was therefore performed (Fig. 4). It showed a light hypercellular matrix with persistence of about 8% of mature plasma cells infiltrate with interstitial distribution (Fig. 4). Plasma cells showed expression of CD138 and restriction of κ light chains by immunohistochemistry, mixed with a lot of crystal-storing histiocytes, positive by CD68R immunostaining.

According to these results, we confirmed that this patient with myeloma with crystal-storing histiocytosis exhibited simultaneous light chain proximal tubulopathy and crystal-storing histiocytosis, which were attributed to monoclonal κ light chains.

In a condition of partial remission according to IMWG 2006 recommendation [14], VTD therapy was continued until the sixth cycle. After the sixth cycle the urinary light chain kappa further loweredto 1010 mg/24h, Free light chain kappa/lamba ratio was reduced to 26. Creatinine levels were 1.36 mg/dL. At present, still in a condition of partial remission, the patient is waiting to proceed with autologous hematopoietic stem cells mobilization and harvest, followed by high dose chemotherapy with autologous transplantation.

Discussion

Multiple myeloma often involves the kidney and results in various light microscopic and ultrastructural entities falling under the umbrella of monoclonal gammopathy-associated renal pathology [10]. Renal damage, most commonly detected as an asymptomatic elevation in serum creatinine, is the second leading cause of death in myeloma and 10-20% will require dialysis [4]. Precipitated monoclonal immunoglobulins in the kidney exhibits various forms, including fibrils (amyloidosis, fibrillary glomerulopathy), microtubules (cryoglobulinemic glomerulonephritis, immunotactoid glomerulopathy), and crystals [10,15]. Monoclonal crystals can take either of the following forms: (a) extracellular crystals within glomerular capillary loops or within interstitial vessel lumens, (b) intracellular crystals within one or more cell types of the kidney which may be glomerular (mesangial cell and visceral epithelial cell) and/or extra-glomerular (usually proximal tubular epithelial cell), and (c) infiltration of histiocytes containing monoclonal crystals in their cytoplasm (crystal-storing histiocytosis)[10,16-18].

Usually, the overload of the proximal tubular epithelial cells lysosomal system is followed by acute tubular necrosis. On rare occasions, the reabsorbed pathogenic LCs form intracellular crystals that impair tubular function, which apart from the rise in serum creatinine, is typically associated with the occurrence of glycosuria, aminoaciduria, hyperuricosuria, hyperphosphaturia, hypercalciuria, and type 2 renal tubular acidosis, typical constituents of an acquired Fanconi syndrome [19-23]. Light chain crystals can also accumulate in other cell types such as podocytes and macrophages, disease processes termed light chain podocytopathy and crystal storing histiocytosis, respectively [3,24-25].

The diagnosis of LCPT can be challenging, and is made by the identification of light chain-restricted intracytoplasmic inclusions within the proximal tubule epithelial cells, which may be quite focal. In the largest series of such cases, Stokes et al. [7] reported 46 cases of LCPT (40 with crystals and 6 without). All 40 cases with crystals were kappa light chain restricted. Stokes reported that most patients had proteinuria (98%) and renal insufficiency (83%). Urinary protein excretion was often heavy (> 1 g/day in 87% and > 3 g/day in 37%), but hypoalbuminemia was not seen. This means the proteinuria consisted predominantly of LC rather than albumin [7]. As in our patient, in up to 85% of patients kidney biopsy showing LCPT is the initial clue to an underlying plasma cell dyscrasia before the disease has come to clinical attention [7]. The underlying hematological disease is MM in 14-33% of cases with the rest being MGUS, SMM, WM, NHL, and CLL [10]. Therefore, the diagnosis of LCPT is crucial for appropriate patient management. The renal biopsy of our patient showed light chain deposition disease, with proximal tubulopathy (κ light chain restricted) and CSH. The bone marrow biopsy showed κ monoclonal plasmacytosis and CSH. Renal immunofluorescence (IF) exhibited no significant glomerular positivity for IgG, IgM, IgA, C3, fibrinogen, k or λ light chains. However, in crystalline LCPT renal injury, IF staining of the light chain on frozen tissue is often negative, which may be due to the light chain epitope hiding in the crystal pattern. However, immunostaining for light chains on paraffin tissue after antigenic retrieval and immuno-electron microscopy study can show monoclonal light chain deposition in the crystals.

Crystal-storing histiocytosis presents with sheets of polygonal and occasionally spindle shaped histiocytes with eccentrically placed, hyperchromatic nuclei with fine chromatin. On close examination or occasionally with polarization, the cytoplasm of the histiocytes will contain needle- like to rhomboid shaped crystals. The intracytoplasmic crystals stain positively for kappa or lambda in most instances, or for heavy chains, although they may occasionally be polyclonal [26]. In the majority of CSH (76-90%) there is an associated underlying lymphoplasmacytic neoplasm expressing κ light chain, although there are case reports with λ and polyclonal crystal formation [27]. In the remaining 10-34% of cases, CSH is associated with other conditions, autoimmune disorders, reactive inflammatory conditions, metabolic disorders, and drugs (e.g. clofazimine, which is used to treat leprosy) [15,27-30]. Crystal-storing histiocytosis is classified into two types, localized and generalized, based on the number of organs involved [10]. The localized form of CSH (58-82% of cases) is confined to a single organ. Generalized CSH (18-42% of cases) involves multiple organ sites (bone marrow, lungs, kidney, lymph nodes, liver, spleen, and gastrointestinal tract) and tends to have a worse prognosis [27-30]. About 20 cases have been reported of renal involvement in CSH up to the date [16,31,32]. In the kidney CSH is rarely a stand-alone pathology, and is in fact, often found co- existing with other morphologic forms of monoclonal renal disease (both crystal and non-crystal forms), including LCPT, usually crystalline subtype, crystalloid glomerulopathy or nephropathy, and cast nephropathy [21]. Conditions mimicking CSH include hemophagocytic lymphohistiocytic syndrome, storage diseases such as Gaucher's, mycobacterial and fungal infections, xanthogranuloma, Langerhans histiocytosis [33]. Similarly, pathologists should be aware that an underlying plasma cell neoplasm or B-cell lymphoma can be masked by the histiocytic infiltrates. The International Kidney and Monoclonal

Gammopathy Research Group recommends chemotherapy or stem cell transplant for LCPT even before worsening hematologic disease occurs [34]. Kidney function showed a general improvement trend in patients who were treated with chemotherapy alone or chemotherapy and stem cell transplantation [7].

In summary, we present a case of LCPT associated with CSH, which is a rare finding on renal biopsy and requires a high index of suspicion, often including immunohistochemical studies on the paraffin- embedded tissue for the diagnosis. Once diagnosis is established, it is necessary to test for underlying lymphoplasmacytic disorders. Correct diagnosis is crucial in driving proper patient management including chemotherapy and/or stem cell transplant for both control of the hematologic process and treatment of kidney disease.

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