

EXCEPTIONAL CASE

Crystalline podocytopathy and tubulopathy linked to kappa light chain deposits in a context of smoldering multiple myeloma

Sébastien Eymieux ^{1,2,3}, Elodie Miquelestorena-Standley ^{3,4},
Nolwenn Rabot⁵, Valentin Maisons^{4,5}, Guy Touchard⁶ and
Emmanuelle Blanchard^{1,2,3}

¹Unité de Biologie cellulaire et microscopie électronique, hôpital Bretonneau CHRU de Tours, Tours, France, ²Inserm U1259 – Morphogénèse et Antigénicité du VIH et des Virus des Hépatites (MAVIVH), Université de Tours, Tours, France, ³Service d'Anatomie et Cytologie Pathologiques, CHRU de Tours, Tours, France, ⁴EA4245-Transplantation, Immunologie, Inflammation, Université de Tours, Tours, France, ⁵Service de Néphrologie, CHRU Tours, Tours, France and ⁶Service d'Anatomie et Cytologie Pathologiques, CHRU Poitiers, Poitiers, France

Correspondence to: Sébastien Eymieux; E-mail: sebastien.eymieux@univ-tours.fr

ABSTRACT

A 42-year-old man with smoldering immunoglobulin G kappa multiple myeloma showed a heavy proteinuria composed of free light chain, prompting performance of a kidney biopsy. Electron microscopy revealed numerous rhomboid-shaped crystals labelled by the anti-kappa in immunogold, notably in the cytoplasm of podocytes, establishing the diagnosis of crystalline podocytopathy. This case illustrates a rare form of monoclonal gammopathy of renal significance, and highlights the key role of electron microscopy and immunogold to better elucidate the location and composition of crystals.

Keywords: crystals, electron microscopy, immunogold, light chain, MGRS, myeloma, podocytopathy

BACKGROUND

The monoclonal gammopathy of renal significance (MGRS) spectrum includes all renal diseases associated with a monoclonal immunoglobulin secreted by a clonal plasma cell. We focus here on MGRS related to monoclonal immunoglobulin deposits, which share a common pathophysiology, and can lead to renal failure. They can affect any renal compartment, and are classified according to the ultrastructural pattern of immunoglobulin

deposits: organized deposits (including fibrillar, microtubular, crystalline and/or inclusionary forms) and non-organized deposits [1]. Cell damage related to crystalline deposits located in the podocytes ('crystalline podocytopathy') has been rarely reported, with only 17 cases formally identified to date, 13 described in a review published in 2018 [2] and 4 additional cases since. Here we present a patient with smoldering multiple myeloma and a light chain-related crystalline podocytopathy associated with tubulopathy.

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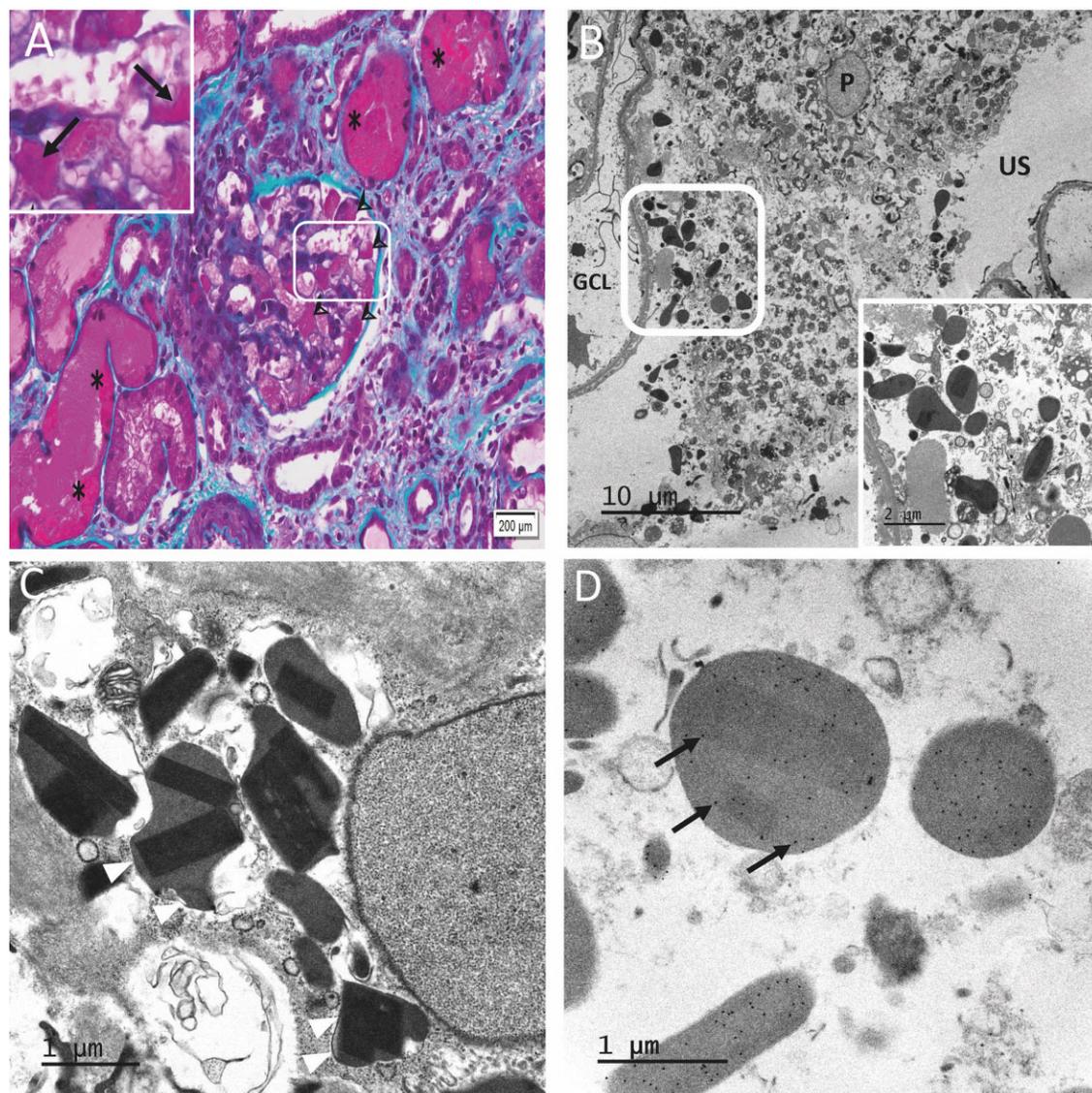


FIGURE 1: Pathology findings. (A) Granular eosinophilic deposits are observed in podocytes cytoplasm (arrows, black arrows in the inset above left) and in tubular cells cytoplasm (stars *) (Masson's trichrome stain $\times 200$). Patient renal biopsy ultrastructural findings in transmission electron microscopy. (B) in glomeruli, podocytes (P) were necrotic and vacuolized ($\times 4000$) (insert below right: crystals surrounded by lysosomal single membrane in podocyte cytoplasm, $\times 15000$). (C) Numerous rhomboid-shaped crystals contained in lysosomal compartments of the mesangial cell ($\times 30000$), white arrowheads = lysosomal membranes. (D) Kappa light-chain crystalline deposits revealed by immuno-electron microscopy ($\times 40000$), black arrows = gold beads conjugated to anti-kappa antibodies ($\times 40000$). Crystals showed no immuno-labelling with the anti-lambda light chain.

CASE REPORT

A 42-year-old man without medical history was admitted for left cervicobrachial neuralgia. Serum protein electrophoresis revealed a spike in the beta-globulin fraction (27.3 g/L) corresponding to a monoclonal immunoglobulin G (IgG) kappa. Bone marrow examination found a more than 10% plasma cell infiltrate and identified clusters of kappa monotypic plasma cells. Magnetic resonance imaging, computed tomography and positron emission tomography scanner showed no suspicious lesions. Serum calcium level (2.36 mmol/L) and serum creatinine (77 $\mu\text{mol/L}$) were normal. There was no biological evidence for Fanconi syndrome, with normal serum potassium level (4.68 mmol/L), normal serum phosphate level (1.09 mmol/L), normal uric

acid level (261 $\mu\text{mol/L}$), absence of metabolic acidosis (serum bicarbonate 27 mmol/L) and no glycosuria on urine test strip. However, nephrotic-range proteinuria (7 g/24 h with free kappa light chain) was found with microscopic haematuria (53 red blood cells/mm³), without nephrotic syndrome (serum albumin 3.7 g/dL). Urine electrophoresis quantified a 1.39 g/L albuminuria, and urine immunofixation revealed Bence-Jones proteinuria composed of free kappa light chains, without free lambda light chains, associated with a monoclonal immunoglobulin band. A renal biopsy was indicated and performed. Diagnosis of smoldering IgG kappa multiple myeloma was established.

Light microscopy examination of renal biopsy included 15 glomeruli, 2 of them displaying focal segmental glomerulosclerosis. Granular eosinophilic deposits were observed in

podocytes and proximal tubular cells on Masson's trichrome staining (Figure 1A). These intracytoplasmic inclusions were particularly noted within podocytes on toluidine-blue stain (Supplementary data, Figure S1). Immunofluorescence (IF) was positive for anti-kappa antibody (Supplementary data, Figure S2A), and negative for anti-lambda antibody (Supplementary data, Figure S2B). Congo red staining did not reveal amyloid deposition. Electron microscopy analysis revealed numerous rhomboid-shaped crystals of various sizes (from 200 nm to 2 µm) surrounded by a membrane located in the cytoplasm of podocytes (Figure 1B), mesangial cells (Figure 1C), glomerular endothelial cells and proximal tubules, and less frequently in the endothelium of peritubular capillaries. Over 57 podocytes were observed on five glomeruli, 56 were necrotic and 54 contained crystals. All podocytes who had crystals were also necrotic. Immunogold technique demonstrated that these crystal structures were composed of kappa light chain (Figure 1D). The diagnosis of kappa light chain-related crystalline podocytopathy and proximal tubulopathy was made.

The patient was initially treated with a chemotherapy associating bortezomib, lenalidomide, dexamethasone and cyclophosphamide. Later on, he received melphalan and autologous peripheral stem cell transplantation due to a partial response to the first treatment. During patient follow-up, renal function remained stable for the next 2 years (respectively: 79.7, 71.7 and 72 µmol/L at 6, 12 and 14 months post-diagnosis), whereas proteinuria progressively decreased (respectively: 5.27, 2.05 and 0.66 g/24 h at 4, 7 and 10 months post-diagnosis). Multiple myeloma has evolved favourably, with a barely detectable minimal residual disease on bone marrow examination 1 year after treatment initiation (plasma cells CD138+/CD38+ <1%).

DISCUSSION

In the present case, this patient with smoldering multiple myeloma presented with light chain proteinuria, normal renal function and absence of Fanconi syndrome. Renal biopsy revealed light chain-related crystalline podocytopathy and proximal tubulopathy, with >98% of necrotic podocytes, and the exact nature and localization of the crystals were confirmed by electron microscopy and immunogold labelling. Light chain crystals are rarely observed in the glomeruli, and are more frequently found in proximal tubular cells in the context of Fanconi syndrome or in tubular lumen in crystalline cast nephropathy. Our observation is consistent with the fact that the intracellular crystallization process seems to be associated with a slowly proliferative hematological malignancy rather than an aggressive myeloma. Regardless of whether monoclonal gammopathy of undetermined significance or myeloma is diagnosed, the risk of renal failure is high and requires treatment of the clone. The iso-type of the light chain crystals is comparable to previous findings concluding that crystalline tubulopathy is mainly associated with kappa light chains, whereas non-crystalline tubulopathy is usually associated with lambda light chains [3]. Finally, this case highlights the key role of electron microscopy in the diag-

nosis of MGRS [4]. Although IF is usually crucial for the diagnosis of MGRS, ultrastructural analysis determines the precise subcellular location of deposits. Immunogold labelling represents an alternative method in case of light chain identification failure by IF, and provides the advantage to formally identify protein component in crystals too small to be visualized by light microscopy. Electron microscopy may provide additional information in difficult cases, and can be crucial to guide the appropriate therapeutic measures [5].

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

PATIENT CONSENT

The patient gave informed consent to publish this case.

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CONFLICT OF INTEREST STATEMENT

None declared.

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