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Non-myeloma light chain cast nephropathy: a multicenter retrospective study on clinicopathological characteristics

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Authorship contribution

All authors participated in the acquisition of data, revised and approved the final version of the manuscript. PI, JPDVH and JO designed the study. PI, and ACM analyzed the data, created the figures and tables and drafted the manuscript.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Data sharing statement

All the data supporting the findings of this study are in the manuscript, figure and supplementary figure.

Keywords

Light chain cast nephropathy

Non-MM mature B-cell neoplasms

Clinico-pathological analysis

To the editor

Kidney injury is a common complication of multiple myeloma (MM)[1], with light chain cast nephropathy (LCCN) being a well described MM defining event correlated with poor outcomes.[2] LCCN results from the precipitation of monoclonal free light chains (FLC) with Tamm-Horsfall protein (THP) in distal tubules.[2] Kidney involvement in other mature B-cell neoplasms with plasmacytic differentiation is very rare when compared to MM.[1] This can result mainly from: monoclonal heavy or light chains deposition in the glomerular basement membrane such as Monoclonal Immunoglobulin Deposition Disease (MIDD), interstitial infiltration of neoplastic lymphoplasmacytic cells, light chain amyloidosis or LCCN.[3,4] In the light of the work of Royal V. and collaborators[2], that described the clinicopathologic predictors of renal outcomes in MM-associated LCCN, we have set out to describe the clinical, biological, and pathological presentation of LCCN in non-MM mature B-cell neoplasms. We also aim to compare the clinicopathologic presentations of MM and non-MM associated LCCN and understand if both diseases have similar renal manifestations and outcomes.

Patients were selected from the renal biopsy databases of the pathology departments of 5 hospitals. Research ethics board approval was granted by the local Ethics Committee of the Assistance Publique Hôpitaux de Paris. Patients were informed about the purpose of the study and gave their assent. Standard processing of renal biopsy samples for light microscopy and immunofluorescence was performed and sections were independently reviewed by 2 pathologists. Pathology variables and scoring definitions were categorized in the same fashion as Royal V. and collaborators[2] to enable the comparison between MM and non-MM light chain cast nephropathy. Continuous variables were described as using mean, median, and interquartile range (IQR) values and categoric

variables were described as frequency and percentage. Mann-Whitney test was used to compare the medians of continuous variables, Fisher Exact Test was performed to compare groups and Kaplan-Meier was performed to analyze overall survival. Pearson's correlation coefficient was used to measure the statistical relationship between two continuous variables.

A total of 23 patients with biopsy-proven non-MM associated LCCN were included. Demographic, clinical, and histopathological characteristics are shown in **Table 1**. The median age was 72 (70-78) years and 56% (n=13) of the patients were male. Fourteen patients were diagnosed with IgM lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, 2 with IgG lymphoplasmacytic lymphoma, 2 with extranodal marginal zone lymphomas with plasmacytic differentiation, 3 with small lymphocytic lymphoma and 2 with diffuse large B-cell lymphoma. Baseline estimated glomerular filtration rate (eGFR, CKD-EPI) defined as renal function prior LCCN was 63 (47-87) mL/min/1.73m2 and eGFR at kidney disease onset was 11.5 (5-15) mL/min/1.73m2.[5] Median proteinuria was 1.28 (0.70-3.08) g/g and 22% (n=5) of the patients had hematuria at presentation. Eighty-three percent (n=19) of the patients presented with KDIGO acute kidney injury (AKI) stage 3, and 44% (n=10) needed dialysis at disease onset. The mean level of FLC at diagnosis was 2237 (437.5-3648.2) mg/L and none of the patients received extracorporeal removal of FLC. Our results show that non-MM neoplasms have a similar clinical presentation, when compared to MM.[2] AKI KDIGO stage 3 was the most common clinical presentation in both entities (82% in MM and 83% in non-MM), with almost half of the patients needing dialysis at disease onset (47% in MM and 44% in non-MM).[2] It is noteworthy that FLC levels at diagnosis in

non-MM LCCN appear lower than those in LCCN associated with MM (2237 vs. 5010 mg/L).[2]

For 13 patients (57%), the diagnosis of both LCCN and hematological malignancy were concomitant and in the other 10 patients (43%) the LCCN diagnosis was made 9.7 (4.4-14.3) years after the hematological malignancy diagnosis at hematological disease relapse or progression. In contrast to MM, where cast nephropathy is most often revealed at the time of hematological diagnosis (92% of the cases before first-line therapy)[2], cast nephropathy in other B-cell neoplasms may in half the cases be an event occurring during follow-up and even several years after the initial diagnosis of the hematological malignancy. This result highlights the need for regular and longitudinal assessment of renal function of patients with mature B-cell neoplasms with plasmacytic differentiation.

The main kidney pathologic findings are summarized in **Table 1** and illustrated in **Figure 1**. The median number of casts per millimeter square was 2.50 (1.18-4.70) in the cortex, 1.25 (0.04-5.17) in the medulla, and 2.35 (1.24-4.70) in the entire kidney biopsy which was close to the findings of Royal et al. (3.2/mm2 in the cortex).[2] The median percentage of globally sclerosed glomeruli was 25% (8-55) and almost half of the patients (48%, n=11) had mild interstitial fibrosis and tubular atrophy (IFTA). All except one patient had acute tubular injury. Most of the patients had interstitial oedema (70%, n=16), tubulitis (74%, n=17), giant cell reaction around the casts (70%, n=16) and tubular rupture (65%, n=15) as previously described in MM LCCN.[2] Only 26% (n=6) of the patients displayed THP extravasation. As myeloma casts are known to be formed through binding to uromodulin, we performed immunohistochemistry analysis

targeting uromodulin.[6] In our patients, the observed monotypic light chain casts were also associated with uromudulin as in MM LCCN (Supplementary Figure 1). Ninety-six percent (n=22) of the patients had cortical interstitial lymphoid infiltrate and 30% (n=7) had medullary interstitial lymphoid infiltrate. Importantly, this infiltration was in most cases due to monoclonal B-cell infiltration observed in 83% (n=19) of the patients. In contrast, in the cohort of 178 patients with MM, only 1.7% (n=3) had interstitial infiltration by neoplastic cells.[2] It should be noted that the extension of the tumor infiltration may be such that it overrides LCCN, especially considering the presence of other conditions secondary to the circulating paraprotein, potentially reducing the detection of hematological malignancy-related LCCN in these patients. The most frequent concomitant kidney pathology was MIDD, which was diagnosed in 22% (n=5) of the patients. Other kidney pathologies were AL amyloidosis, amyloid cast nephropathy and C3 glomerulopathy. In the cohort of 178 patients with MM, 10.6% (n=19) had other kidney diseases, with, as in our cohort, MIDD as the most frequently associated disease (n=11, 6.2%,).[2]

As identified in MM, eGFR at disease onset was inversely correlated with the number of casts per millimeter square in the cortex and medulla combined (r=-0.423, p=0.045).[2] In addition, patients with a number of casts higher than 2/mm^2 in the whole sample, presented with higher serum creatinine (361 +/-330 vs 724 +/- 392 µmol/L, p=0.032) and lower eGFR (20 +/- 12 vs 8 +/- 4 mL/min/1.73m2, p=0,016). We also observed a positive correlation between proteinuria and the number of casts per millimeter square of the total sample (r= 0.558, p=0.009), and between proteinuria and light chain levels (r=0.590, p=0.016). Of interest, FLC level was higher in the group with >25% of IFTA (3793 mg/L) when compared with the group with <25% of IFTA (1101.5 mg/L),

$p<0.05$. This is similar to the findings of V. Royal et al.[2] and further supports the hypothesis of a chronic profibrotic role for light-chain proteinuria, as mentioned by WZ Ying et al.[7] Of note, the percentage of globally sclerotic glomeruli did not correlate with onset eGFR or proteinuria, but it did correlate with baseline eGFR (r=-0.694, p=0.004) and serum creatinine (r=0.630, p=0.012). There was no statistically significant difference in terms of presenting eGFR or serum creatinine between the patients who had absence or presence of giant cell reaction around casts, tubulitis, interstitial oedema, tubular rupture, THP extravasation or IFTA.

Of particular importance, 12 patients (52%) died during the follow-up period, with a median survival of 15 months (3-48) comparable to that of patients with MM associated LCCN (103 deaths, 58%, median survival of 13 months).[2] In addition, all patients requiring dialysis at the time of diagnosis (n=10) progressed to end-stage renal failure or died (n=6). Among alive patients at last follow up (n=10), median eGFR at presentation was 13.5 (4-21) mL/min and 40% (n=4) of the patients required hemodialysis at presentation. All these 4 patients remained under hemodialysis at last follow-up. None of the patients that did not require hemodialysis at disease onset (n=6) progressed to end stage renal disease and presented a median eGFR at last follow-up of 36.5 (27-47) mL/min. The eGFR delta between initial and final eGFR in these 6 patients represented an increase of 14.5 (11-20) ml/min, i.e. a median increase of 61%. Thus, although lymphoplasmacytic lymphomas are considered hematological malignancies with a better overall prognosis than myeloma[8,9], the presence of associated LCCN considerably worsens the survival of patients, with mortality rates comparable to myeloma associated LCCN.[2] It is therefore crucial to diagnose this renal complication early in all patients with lymphoplasmacytic lymphomas.

This multicenter study represents the most extensive investigation of its kind to examine and delineate the clinical and pathological attributes of non-MM LCCN while drawing comparisons with MM LCCN. However, the limited number of patients in our study, attributed to the rarity of the disease and inherent to the retrospective nature of the study, presented a challenge in achieving statistically significant results and identifying reliable prognostic markers. Overall, our pathological analysis and correlation with clinical and biological data at presentation, were very close to those of patients with MM, particularly with regard to the number of casts and correlation with initial renal dysfunction. More importantly, we show that non-MM LCCN is associated with poor survival as in MM.

Finally, with regard to clinicians and pathologists, this study allowed to identify 3 important points. First, this study emphasizes the need of a close and longitudinal assessment of kidney function in patients with mature B-cell neoplasms with plasmacytic differentiation. Unlike MM LCCN, non-MM/lymphoma LCCN is often not concomitant with the diagnosis of hematological malignancy, and often develops later (43% of our cases). Secondly, it should raise pathologists' awareness of the need to look for casts in lymphoma patients, as LCCN is classically associated with myeloma and not lymphomatous disorders. Lastly, it should also sensitize pathologists to systematically look for casts even in the presence of more exuberant histological features that may overlap, such as tumor cell infiltration (83% of our cases) and/or glomerular lesions (MIDD), which could cause them to miss the most important lesion in terms of outcome.

References

1. Leung N, Bridoux F, Nasr SH. Monoclonal Gammopathy of Renal Significance. N Engl J Med. 2021;384(20):1931-1941.
2. Royal V, Leung N, Troyanov S, et al. Clinicopathologic predictors of renal outcomes in light chain cast nephropathy: a multicenter retrospective study. Blood. 2020;135(21):1833-1846.
3. Vos JM, Gustine J, Rennke HG, et al. Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes. Br J Haematol. 2016;175(4):623-630.
4. Uppal NN, Monga D, Vernace MA, et al. Kidney diseases associated with Waldenström macroglobulinemia. Nephrol Dial Transplant. 2019;34(10):1644-1652.
5. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
6. Sanders PW. Mechanisms of light chain injury along the tubular nephron. J Am Soc Nephrol. 2012;23(11):1777-1781.
7. Ying WZ, Li X, Rangarajan S, Feng W, Curtis LM, Sanders PW. Immunoglobulin light chains generate proinflammatory and profibrotic kidney injury. J Clin Invest. 2019;129(7):2792-2806.
8. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-1253.
9. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.

Table

Table 1 - Demographic, baseline renal and hematological characteristics and histological findings

Characteristic:	Patients (n = 23)
Demographic characteristics	
Age, y	72 (70-78)
Male sex, %	56 (n=13)
Renal characteristics	
Baseline eGFR, ml/min/1.73m2	63 (47-87)
eGFR at disease onset, ml/min/1.73m2	11.5 (5-15)
AKI KDIGO stage (unknown, 1, 2, 3), %	4, 4, 9, 83
Dialysis dependence at presentation, %	44 (n=10)
Proteinuria, g/24h	1.28 (0.70-3.08)
Albuminuria fraction, % (n=6)	18 (3-27)
Hematuria, %	22 (n=5)
Hematological characteristics	
Prior LCCN diagnosis, %	44 (n=10)
Waldenstrom macroglobulinemia, %	60.9 (n=14)
Small lymphocytic lymphoma	13 (n=3)
IgG lymphoplasmacytic lymphoma	8.7 (n=2)
Extranodal marginal zone lymphomas	8.7 (n=2)
Diffuse large B-cell lymphoma	8.7 (n=2)
Type of heavy chains (IgA, IgM, IgG, none), %	9, 57, 30, 4
Quantification of monoclonal spike, g/L	22.2 (7,7-37,4)
κ light chain, %	74 (n=17)
λ light chain, %	26 (n=6)
FLC level, mg/L	2237 (437,5-3648,2)
Pathology findings	
Globally sclerosed glomeruli, %	25 (8-55)
Interstitial fibrosis and tubular atrophy, (0, 1+, 2+, 3+, no data), %	17, 48, 22, 9, 4
Cortical interstitial inflammation (0, 1+, 2+, no cortex), %	4, 44, 52, 0
Medullary interstitial inflammation (0, 1+, 2+, no medulla), %	9, 17, 13, 61
THP in Bowman's space, %	4 (n=1)
Acute tubular injury, %	96 (n=22)
Interstitial oedema, %	70 (n=16)
Tubulitis, %	74 (n=17)
Giant cell reaction around casts, %	70 (n=16)
Tubular rupture, %	65 (n=15)
THP extravasation, %	26 (n=6)
Mean number of cortical cast/mm2	4,0 ± 3,8
Mean number of medullary cast/mm2	2,8 ± 4,1
Arteriosclerosis (0, 1+, 2+, 3+, no arteries), %	13, 22, 26, 30, 9
Arteriolar hyalinosis (0, 1+, 2+, 3+), %	44, 17, 13, 26
Monoclonal B-cell infiltration, %	83 (n=19)

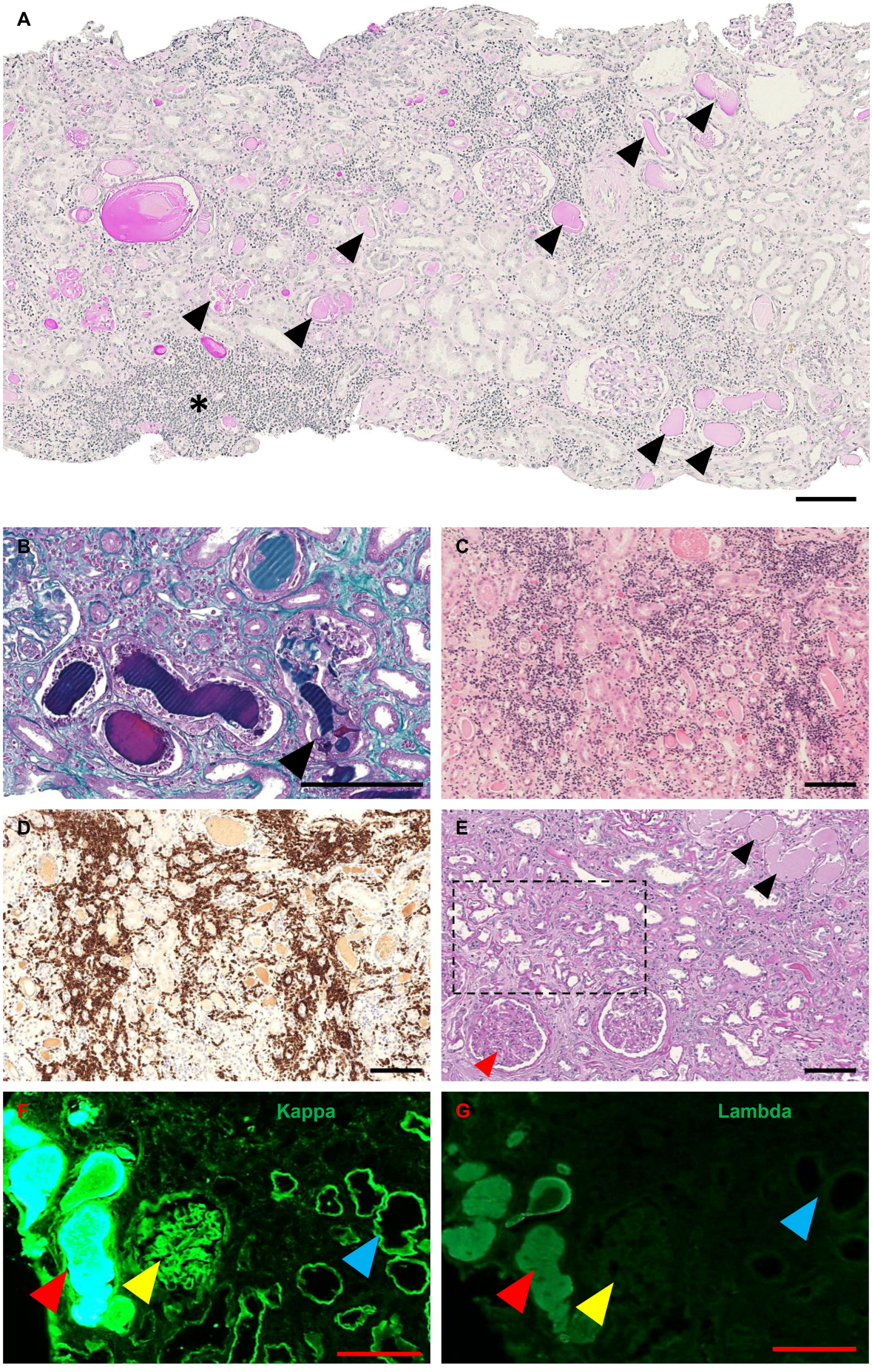
Other kidney disease, %	
AL Amyloidosis	4 (n=1)
Amyloid cast	4 (n=1)
C3 Glomerulopathy	4 (n=1)
MIDD	22 (n=5)

y: year; eGFR: estimated glomerular filtration rate; AKI: acute kidney injury; KDIGO: kidney disease improving global outcomes; LCCN: light chain cast nephropathy; FLC: free light chain; THP: Tamm–Horsfall protein; MIDD: monoclonal immunoglobulin deposition disease.

Figure legend

Figure 1. Pathology illustrations.

A. Representative image of patient kidney biopsies using light microscopy with periodic acid–Schiff staining (PAS), showing multiple pale tubular casts with PAS staining (black arrow) and areas of interstitial infiltration (black asterisk). **B.** Light microscopy using Masson's trichrome staining showing typical polychromatophilic cast with giant cell reaction around a fractured cast (black arrow). **C.** Light microscopy using hematoxylin eosin staining showing diffuse interstitial lymphoma infiltration**. D.** Immunohistochemistry analysis targeting CD79A showing diffuse interstitial B-cell lymphoma infiltration. **E.** Light microscopy using PAS staining from a patient with Monoclonal Immunoglobulin Deposition Disease (MIDD) and associated cast nephropathy showing PAS-positive mesangial expansion (red arrow) and PAS-positive tubular basement membrane thickening (black square) together with the presence of PAS-negative tubular casts (black arrow). **F. and G.** Immunofluorescence analyses of a patient with MIDD and associated cast nephropathy using anti-kappa and anti-lambda antibodies showing monotypic kappa light chain staining within: tubular cast (red arrow), glomerular mesangium (yellow arrow) and tubular basement membrane (blue arrow). Scale Bar 100µm.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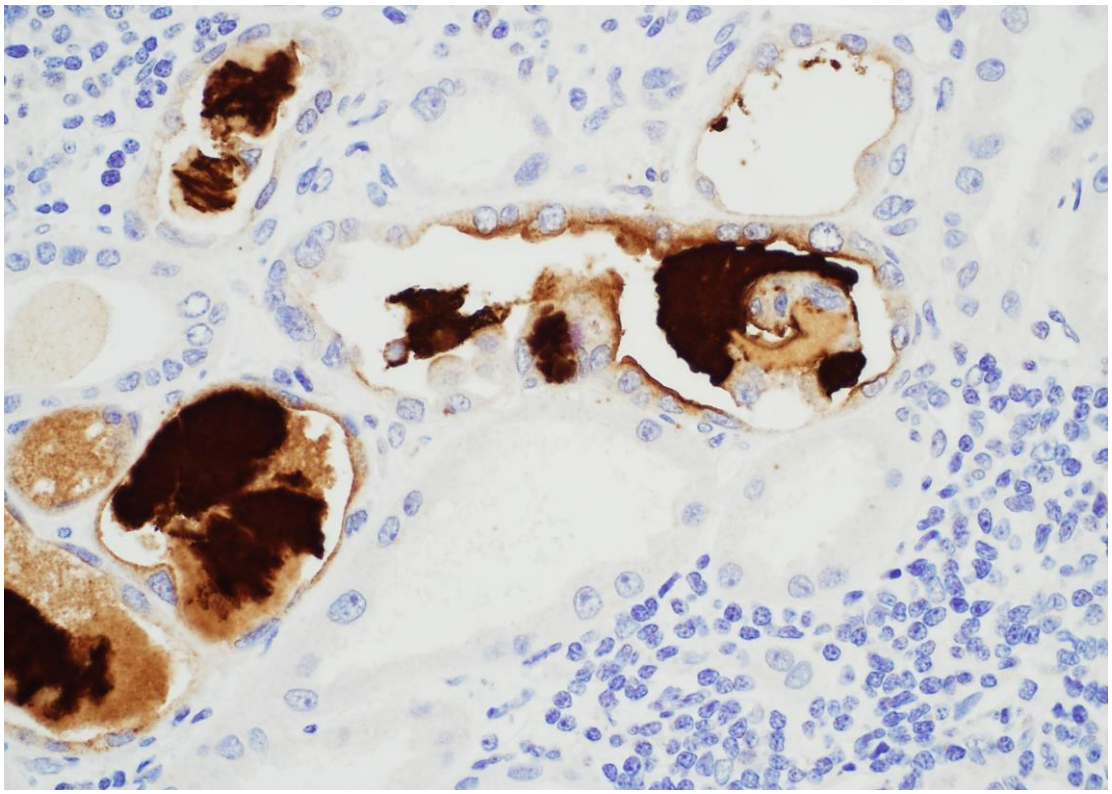

Supplementary Figure 1: Immunohistochemistry of uromodulin

Representative image of immunohistochemistry targeting uromodulin showing its association to casts identified in the lumen of tubular sections.