Authors

Inna MOHAMADOU, MD¹

David BUOB, PhD¹

Marion RABANT, PhD²

Jérémy PICHON, MD¹

Stéphane GAUDRY, PhD³

Yosu LUQUE, PhD¹

Eric RONDEAU, PhD¹

Isabelle BROCHERIOU, PhD¹

Cédric RAFAT, MD¹

¹ Assistance Publique des Hôpitaux de Paris – Sorbonne Université

² Assistance Publique des Hôpitaux de Paris – Université Paris-Descartes

³ Assistance Publique des Hôpitaux de Paris – Université Paris XIII

Corresponding author: Inna MOHAMADOU – inna.mohamadou@aphp.fr

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The Case: Acute kidney injury associated with chronic myelomonocytic leukemia

A 70-year-old man with a history of high blood pressure and multiple ischemic strokes was diagnosed with stage 2 chronic myelomonocytic leukemia (CMML) in 2014. At diagnosis, estimated glomerular filtration rate (eGFR) was normal (100 ml/min/1,73m²). Bone marrow aspiration showed 15% blasts, for which azacytidine was prescribed. The patient refused the recommended treatment, and hydroxyurea was introduced instead.

He was readmitted four years later with acute kidney injury. On physical examination, blood pressure was 145/98 mmHg, and moderate hepatosplenomegaly was noted. Laboratory tests revealed serum creatinine (SCr) 477 $\mu\text{mol.L}^{-1}$, low levels of plasma potassium (3.4 mmol L⁻¹), uric acid (174 $\mu\text{mol.L}^{-1}$) and phosphate (0,74 mmol.L⁻¹), whereas calcium level and bicarbonate levels were normal. There was evidence of partial Fanconi syndrome with elevated potassium transtubular potassium gradient (11), elevated fractional excretion of uric acid (34%, normal < 10%) and phosphate (59%, normal < 20%). Urine proteinuria/urine creatinine ratio was of 220 mg.mmol⁻¹ with 25% of albumin, and increased level of retinol binding protein/urine creatinine (13 mg.mmol⁻¹). Hematological studies showed thrombocytosis (615 G.L¹) and leukocytosis (27.1 G.L¹), with elevated neutrophils (19.2 G.L¹) and monocytes (6.2 G.L¹).

Light microscopy of kidney biopsy is shown in figure 1.

What is the diagnosis?

The Diagnosis: Lysozyme induced nephropathy

The kidney biopsy revealed diffuse tubular injury, which consisted in a flattening of the proximal tubular epithelium (figure 1a), and the presence of sparse cytoplasmic droplets (figure 1b). There was no interstitial fibrosis or cellular infiltrate. Glomeruli were normal. Immunohistochemistry with anti-lysozyme antibody yielded diffuse granular cytoplasmic reactivity in the proximal tubule (figure 2a) with reinforcement of the cytoplasmic droplets (figure 2b). The biopsy findings along with markedly elevated levels of lysozyme in the plasma (120 mg.L^{-1} ; N: $5\text{--}10 \text{ mg.L}^{-1}$) and urine (200 mg.L^{-1} ; N $<2 \text{ mg.L}^{-1}$), led to the diagnosis of lysozyme induced nephropathy (LN) with features of the Fanconi syndrome.

Lysozyme has a relatively low molecular weight (15 kDa) and is freely filtered by the glomerulus. In the proximal tubular epithelial cells (PTEC), lysozyme is endocytosed via megalin-cubilin receptors, and ultimately undergoes lysosome-mediated degradation (1). Evidence of tubular injury occurs when plasma lysozyme concentration exceeds 3 times the normal concentration of plasma lysozyme (2) and PTEC typically display hypereosinophilic cytoplasm due to the presence of PAS-positive granules. As lysozyme is trafficked in lysosomes, it can be hypothesized that lysozyme disrupts autophagy in PTEC although further studies are required to properly understand the physiological mechanisms underlying LN.

LN is a rare renal complication appearing in the face of an increased lysozyme production, a manifestation of diseases in which the common denominator includes monocyte-macrophage dysfunction. The commonest entity associated with LN is CMML, followed by acute myeloid leukemia and sarcoidosis (3).

Treatment of LN relies solely on the treatment of the underlying cause. In CMML, allogeneic stem cell transplantation is curative, and hypomethylating agents are used as alternative therapy. Our patient was treated with azacytidine and ruxolotinib. Kidney function improved as white blood cells counts normalized. After one year of treatment, SCr was $92 \text{ }\mu\text{mol.L}^{-1}$ (eGFR $83 \text{ ml/min/1.73m}^2$), and signs of proximal tubular dysfunction had resolved.

Even though our patient presented with acute kidney injury, most of the rare cases of LN published in the literature to date are characterized by chronic kidney disease, highlighting the potential for severe, irreversible renal disease. Signs of proximal tubular dysfunction associated to LN may be subtle and must be looked for carefully (e.g. Fanconi syndrome), even in the absence of renal impairment.

Figure 1a: Tubular injury with epithelial flattening (hematoxylin-eosin, magnification x 100)

Figure 1b: Sparse intracytoplasmic droplets (hematoxylin-eosin, magnification x 400)

Figure 2a: Lysozyme detection within the cytoplasm of proximal tubular cells (immunohistochemistry with anti-lysozyme antibody, magnification x 100)

Figure 2b: Strong staining of the intracytoplasmic droplets with anti-lysozyme antibody (immunohistochemistry with anti-lysozyme antibody, magnification x 400)

Disclosures:
Nothing to disclose.

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Figure 1a

Figure 1b

Figure 2a

Figure 2b