The Case | An unusual cause of renal vascular thrombi after kidney transplantation

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In 2008, a 36-year-old woman presented with edema of the lower limbs. Kidney function was normal. Urinalysis revealed nonselective glomerular proteinuria, with hematuria. The classical immune and serological workup was noncontributive. Renal biopsy revealed an immune complex–mediated membranoproliferative glomerulonephritis, associated with the presence of intracapillary thrombi. Hemodialysis was initiated in 2010 after multiple unsuccessful treatments with immunosuppressive agents. A short time before that, the patient suffered from an episode of jejunitis.

In 2013, the patient underwent a first kidney transplant (KTx). *Per cause* graft biopsy at D4 showed thrombi in arterioles and glomerular capillaries. Given the presence of an historical donor-specific antibody, a diagnosis of C4d-negative antibody-mediated rejection was made. No immune or alternative complement pathway disorders nor cryoglobulinemia was identified. Plasmapheresis was initiated in association with high doses of methylprednisolone. No improvement of graft function was noted, and the patient returned to chronic hemodialysis rapidly after KTx. A thorough hematological workup regarding a predominant λ IgA on serum immunofixation did not detect abnormal serum κ/λ-free light chains nor plasma cell disorder by the means of bone marrow biopsy. Note that in 2015, the patient had an episode of necrotizing vasculitis of the lower limbs.

In 2017, a second KTx was performed. Graft function rapidly deteriorated, leading to *per cause* graft biopsy at D4. Histological examination revealed the massive presence of thrombi in the arterioles and glomerular capillaries. The analysis of the thrombi by immunohistochemistry and immunofluorescence highlighted a predominant positivity for IgA, fibrinogen, and λ light chains. Ultrastructural analysis by electron microscopy was performed (Figure 1; Supplementary Figure S1).

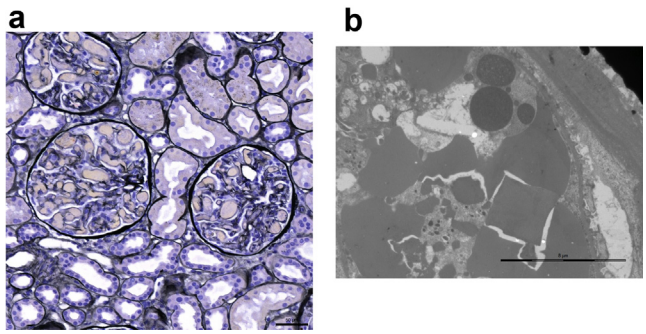

Figure 1 | Representative histological findings of the kidney graft biopsy performed in 2017. (**a**) Thrombi in the glomerular capillary loops (Jones methenamine silver stain). (**b**) Electron microscopy of a glomerular capillary loop. Bars = (**a**) 50 μm and (**b**) 8 μm. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

What is your diagnosis?

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The Diagnosis | **Monoclonal gammopathy of renal significance**

A diagnosis of monoclonal gammopathy of renal significance presenting as IgA λ crystalglobulinemia was made on the basis of the typical crystalline structure of the intravascular Ig deposits in electron microscopy.[1] *A posteriori* ultrastructural examination of the failed kidney graft in 2013 confirmed the presence of similar intravascular Ig deposits, with a predominant immunoreactivity of the thrombi for IgA and λ light chains. Additional hematological investigations revealed the fluctuating presence of an IgA λ monoclonal protein at serum protein immunofixation, with a normal urinary and serum κ/λ light chain ratio. A bone marrow aspirate and biopsy showed 0.7% plasma cells, with no evidence of myeloma (Table 1). The patient was treated by 10 cycles of the bortezomib-cyclophosphamide-dexamethasone regimen. A kidney biopsy performed in 2019 showed the disappearance of crystalglobulins, with a kidney graft still functional in 2021.

Kidney injury associated with crystalglobulinemia is a rare entity of monoclonal gammopathy of renal significance, characterized by the spontaneous crystallization of the monoclonal Ig in the microvasculature. The intravascular deposition of crystalglobulins may cause endothelial injury, occlusion of small vessels, thrombosis, and/or vasculitis, leading to various systemic manifestations.[1,2] Classically, crystalglobulinemia-associated nephropathy, under examination by light microscopy, shows large extracellular eosinophilic material in the lumen of glomerular capillaries and/or arterioles, associated or not with secondary thrombosis.[1–3] The differential diagnosis is challenging because the key distinguishing feature relies on a typical crystalline structure of the intravascular Ig deposits on electron microscopy. The present case report demonstrates the absolute necessity of early and appropriate management to control the clonal plasma cell proliferation. Treatment recommendations for monoclonal gammopathy of renal significance–related kidney disease are currently extrapolated from equivalent malignant diseases, because no clinical trials have been conducted thus far.[1] The follow-up biopsy after treatment in our case confirmed successful kidney recovery after a combination of plasmapheresis and chemotherapeutic regimens.

Few data are currently available concerning the risk of crystalglobulinemia recurrence after KTx. We report here a rare case of crystalglobulin-induced nephropathy that presented twice immediately after KTx, leading to dramatic acute graft dysfunction. The rapidity of kidney damage may potentially be explained by an increased sensitivity to the intravascular deposits of monoclonal Ig because of the ischemic post-KTx environment as well as by the tacrolimus-associated intrarenal vasoconstriction.[3]

The identification of (pseudo-)thrombi in *per cause* graft biopsy in the absence of other criteria for antibody-mediated rejection should (i) alert the clinician to suspect monoclonal gammopathy of renal significance in the case of paraproteinemia and history of skin lesions and (ii) prompt an ultrastructural examination.

Table 1 | Most relevant biological and hematological results at the time of native kidney and kidney graft biopsies

	Native kidneys	First KTx	Second KTx
Data	**2008**	**2013**	**2017**
Biological features			
Hemoglobin, g/dl	12.1	7.9	9.6
Platelets, per mm^3	375×10^3	258×10^3	164×10^3
Schizocytes, %	ND	0.1	0.2
Haptoglobin, g/l	ND	1.90	1.60
LDH, IU/l	226	265	173
SCr, mg/dl	0.85	5.19	2.41
C3c, g/l	1.18	0.85	0.86
C4, g/l	0.12	0.153	0.09
ANCA	Negative	Negative	ND
AAN	Negative	Negative	Negative
Proteinuria, mg/g UCr	1697	12,740	2345
Hematuria	+	+	+
Hematological workup			
Gamma globulin			
IgA, g/l	2.09	1.78	1.29
IgM, g/l	4.25	7.84	4.57
IgG, g/l	3.28	0.57	0.80
Serum protein IF	No monoclonal protein	Predominant IgA λ banding	IgA λ monoclonal protein (intermittent)
Cryoglobulinemia	Negative	Negative	Light positivity
Urinary κ/λ ratio	1.43	ND	1.64
Serum κ/λ light chain ratio	ND	0.85	1.03
+		**2015**	**2017**
Bone marrow aspirate		<2% plasma cells	<1% plasma cells

AAN, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic autoantibody; IF, immunofixation; KTx, kidney transplant; LDH, lactate dehydrogenase; ND, not done; SCr, serum creatinine; UCr, urine creatinine.

DISCLOSURE

PE and FJ are fellows of the Fonds National de la Recherche Scientifique. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. (**A**) Thrombi in the glomerular capillary loops (hematoxylin and eosin staining). (**B**) Occlusion of the glomerular arteriole lumen (Jones methenamine silver stain). (**C**) IgA immunohistochemistry showing positivity of the glomerular intravascular deposits. Bars = 50 μm.

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