

# Bilateral Kidney Infarction Due to Primary AL Amyloidosis

## *A First Case Report*

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**Abstract:** Primary Amyloid Light-chain (AL) amyloidosis is a rare form of plasma cell dyscrasia characterized by tissue deposition of monoclonal immunoglobulin light chain. Kidney involvement is the most frequent manifestation, and patients usually present with glomerular disease.

We report an exceptional case of bilateral kidney infarcts caused by AL amyloidosis. A 34-years-old man presented with progressive dyspnea, loin pain, recurrent macroscopic hematuria, and acute kidney injury. Computed tomography showed bilateral kidney infarcts.

The diagnosis of AL amyloidosis was established on the kidney biopsy with the characterization of major vascular amyloid deposits that selectively stained with antilambda light chain antibody. An amyloid restrictive cardiomyopathy was also present, responsible for the life-threatening conduction disturbance, but without patent cardioembolic disease. The patient then underwent emergency heart transplantation, followed by a conventional chemotherapy with bortezomib, melphalan, and dexamethasone. More than 3 years later, the patient has subnormal renal function, a well-functioning heart transplant, and a sustained hematologic response.

In addition to the very uncommon presentation, this case illustrates the tremendous progress that has occurred in the management of severe forms of AL amyloidosis.

(*Medicine* 94(17):e777)

**Abbreviations:** ASCT = autologous stem cell transplantation, BNP = brain natriuretic peptide,  $GFR_{MDRD}$  = glomerular filtration rate estimated by the MDRD equation.

## INTRODUCTION

Primary Amyloid Light-chain (AL) amyloidosis is a rare form of plasma cell dyscrasia characterized by tissue deposits commonly made of monoclonal immunoglobulin light chain.<sup>1</sup> Involvement of the heart, kidney, liver, and autonomic nervous systems is responsible for the poor prognosis of AL amyloidosis. Patients' survival significantly improved during

the last 15 years with the use of more effective conventional-dose chemotherapy and/or autologous stem cell transplantation (ASCT).<sup>2</sup> We report an unusual case of AL amyloidosis with bilateral kidney infarcts at presentation and predominantly renal vascular amyloid deposits, associated with a severe cardiomyopathy. This case is exceptional because it first reports bilateral kidney infarcts caused by AL amyloidosis and illustrates the groundbreaking advances in the therapy of this dreadful disease.

## CASE REPORT

A 34-year-old man was referred because of acute pain of the left flank associated with macroscopic hematuria. A painless macroscopic episode was recorded 6 months earlier. Two months before admission the patient underwent a cardiac evaluation for progressive dyspnea, thoracic pain, and palpitations. Transthoracic ultrasound revealed severe hypertrophic cardiomyopathy with biventricular wall thickening and altered left ventricular ejection fraction (45%).

On admission, physical examination showed a low blood pressure of 100/50 mmHg and New York Heart Association class II heart failure. Electrocardiography showed low voltage in the limb leads without conduction defect. Acute kidney injury was present with serum creatinine level of 1.9 mg/dL (167  $\mu$ mol/L, glomerular filtration rate estimated by the Modification of the Diet in Renal Disease (MDRD) equation [ $GFR_{MDRD}$ ] 44 mL/min/1.73 m<sup>2</sup>), abnormal urine protein-creatinine (180 mg/mmol), and albumin-creatinine ratios (92 mg/mmol). Urine excretion of a monoclonal lambda light chain (15% of total proteinuria) associated with serum increase of free lambda light chain (912 mg/L, N 5.7–26.3) was detected. Serum lactate dehydrogenase level was 10-fold upper the normal level, brain natriuretic peptide (BNP) was 1751 ng/L (N < 100) with troponin I elevation at 0.52  $\mu$ g/L (N < 0.05). Blood cell count and serum electrolytes were normal. Renal ultrasound at presentation was unremarkable. A contrast-enhanced abdominal Computed tomography-scan performed 2 days after admission because of the recurrence of flank pains



**FIGURE 1.** Abdominal CT-scan showing multifocal bilateral renal infarcts.

Editor: Costas Fourtounas.

Received: January 30, 2015; revised: March 10, 2015; accepted: March 23, 2015.

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The authors have no funding and conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000777

showed multifocal bilateral renal infarcts (Figure 1), with normal renal artery and vein, and liver and spleen enlargement. Repeated transoesophageal echocardiography showed increased echogenicity and thickening of the myocardium that was highly suggestive for amyloid infiltration, without intracardiac thrombus. Mitral and aortic valve were also prominent. Holter monitor did not document paroxysmic arrhythmia or conduction defects.

A kidney biopsy was performed (Figure 2). Light microscopy showed normal glomeruli and large areas of acute tubular necrosis associated with interstitial edema and nonspecific inflammatory infiltrates. No arteriolar thrombosis was observed. Congo red stain disclosed vascular amyloid deposits, and immunofluorescence showed positive staining for lambda light chain in the kidney vessel walls only, with no labeling of the glomeruli. Electron microscopy examination confirmed fibrillary organization of the vascular deposits, but also disclosed fine fibrillar deposits in the glomerular basement membrane.

A diagnosis of AL amyloidosis was made. A search for coexisting B-cell malignancy, including multiple myeloma, was negative. Due to the advanced amyloid cardiomyopathy, the patient was referred for emergency heart transplantation, which was performed 2 weeks after the admission. Native heart showed hypertrophic cardiomyopathy with a weight of 604 g. There were no macroscopic lesion in pericardium, coronary arteries, and myocardium. Endocardium was white and mitral valve was thickened. On microscopy, amyloid deposits were present on fat tissue, epicardial vessels, and myocardium. He subsequently received chemotherapy with high-dose prednisone ( $60 \text{ mg/m}^2$ ), melphalan ( $9 \text{ mg/m}^2$ ), and bortezomib ( $1.3 \text{ mg/m}^2$  twice weekly every 21 days) for 4 cycles and then bortezomib and dexamethasone ( $10 \text{ mg/m}^2$ ) for 6 cycles between September 2009 and October 2011. On last follow-up, 40 months after cardiac surgery, the patient had a stable chronic kidney disease stage 3 with serum creatinine of  $139 \mu\text{mol/L}$  ( $\text{GFR}_{\text{MDRD}} 50 \text{ mL/min/1.73 m}^2$ ), a protein-creatinine ratio of  $40 \text{ mg/mmolC}$ , and a sustained remission of AL amyloidosis with normal level of serum free light chain, normal troponin I, and N-terminal pro-brain natriuretic peptide.

The patient gave his informed consent. The kidney biopsy tissue collection was approved by the Commission informatique et liberté and declared to the French Ministry of Health.

## DISCUSSION

We present an exceptional case of AL amyloidosis remarkable for its unusual clinical presentation with bilateral kidney infarcts, predominant amyloid vascular deposits on the kidney biopsy and favorable outcome after heart transplantation and chemotherapy.

Renal involvement is the most frequent manifestation of AL amyloidosis, with proteinuria, mainly composed of albumin, being detected in 55% of patients at presentation.<sup>3</sup> Combined glomerular and vascular amyloid deposits are common, whereas restricted vessel involvement is observed in <10% of kidney biopsy specimens and is usually associated with low level of proteinuria.<sup>4</sup> In the present case, the renal presentation was very unusual with hematuria, loin pain, and acute renal failure related to multiple renal infarcts. Renal amyloid deposits were restricted to vessels by light microscopy. However, significant albuminuria was present, suggesting the presence of glomerular deposits that were not detected by Congo red stain

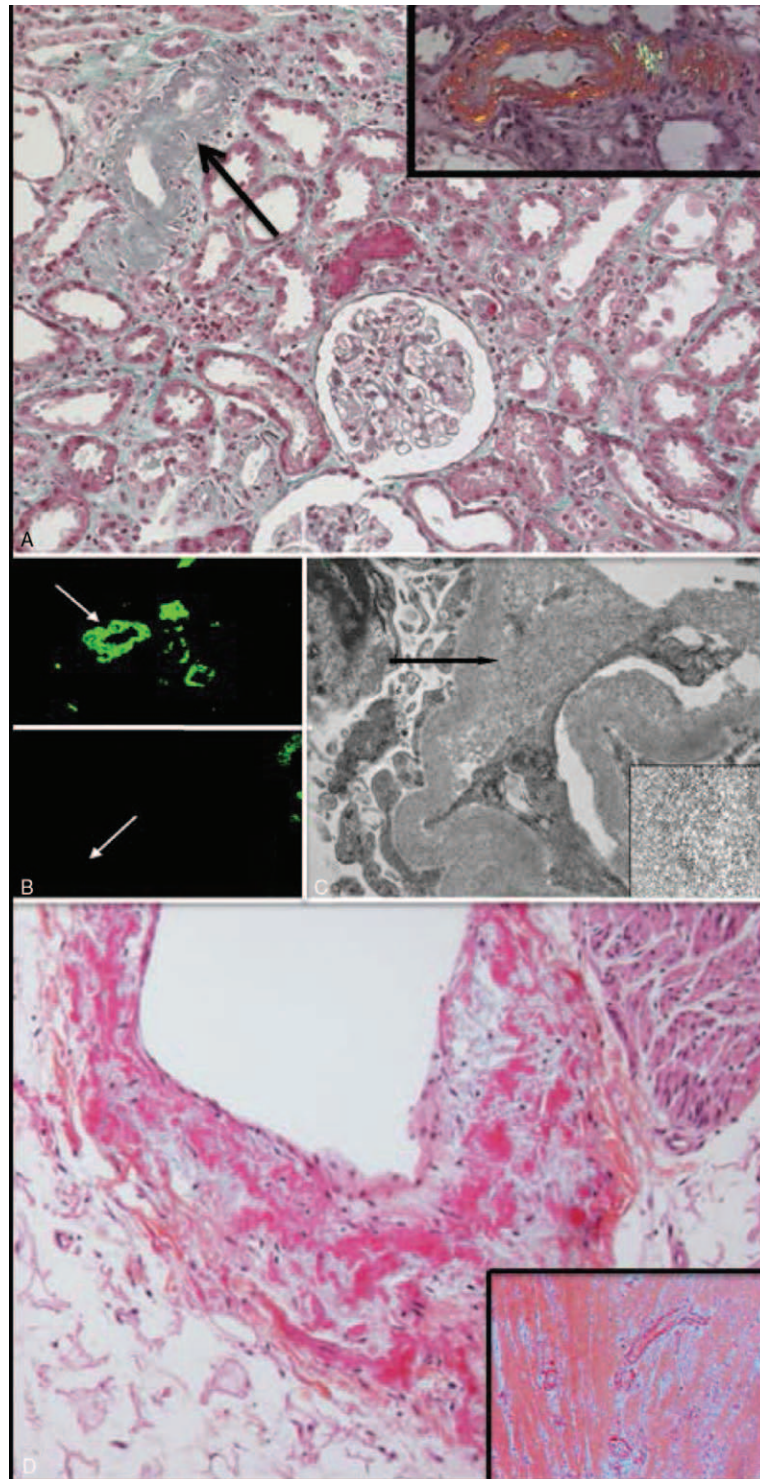
and immunofluorescence examination but only found by electron microscopy.

Laws governing the tissue tropism of amyloidogenic light chains have not yet been elucidated. The primary structure of the light chain may play a central role in determining tissue localization. The strong association of VLambda 6a light chains with predominant kidney involvement comforts this hypothesis.<sup>5</sup> The particular tropism of VLambda 6a light chains for the kidney might be explained by a receptor-mediated interaction with mesangial cells. Recently, an association between dominant cardiac involvement and the *gene IGLV1-44 and l. 3 family* has been described.<sup>6</sup> However, other factors such as somatic mutations and post-translational modifications are likely to be involved.

Arterial thromboembolic events are rare in AL amyloidosis and mainly responsible for ischemic stroke, although peripheral arterial occlusions have been reported, affecting mesenteric, iliac artery, or optical nerve arteries.<sup>7</sup> To our knowledge, renal infarcts have not been previously reported. Amyloid cardiomyopathy may promote thromboembolic events, mainly due to intracardiac thrombus formation that is detected by transoesophageal echocardiography or at autopsy in 27% and 33% of patients, respectively.<sup>8</sup> Atrial fibrillation, left ventricular diastolic dysfunction, and increased right ventricular wall thickness are associated with increased risk of intracardiac thrombus. However, in some patients, cardiac evaluation failed to detect an intracardiac thrombus, as in the present case. Hypercoagulability states have been identified as contributing factor to arterial thromboembolic events in AL amyloidosis, in patients receiving thalidomide and oestrogen, or presenting with extracellular volume disturbance and nephrotic syndrome. Moreover, myocardial infarcts caused by coronary obstruction related to extensive vascular amyloid deposits have been reported.<sup>9</sup> In our case, the respective contribution of renal vascular amyloid lesions and cardioembolic events in the occurrence of renal infarcts is difficult to assess. Although our patient presented with clinical, biochemical, and echocardiographic evidence of severe amyloid cardiomyopathy, transoesophageal echocardiography, and histological examination of native heart at transplantation failed to detect intracardiac thrombus. Conversely, no arteriolar thrombosis was observed in the biopsy kidney specimen despite the presence of vascular amyloid deposits.

In addition to its unusual renal presentation, this case underlines that the sequential therapeutic approach of heart transplantation followed by high-dose dexamethasone-based chemotherapy with or without ASCT is feasible. Such strategy should therefore be discussed in selected patients with predominant, severe cardiac involvement at diagnosis, which is the main prognostic factor in AL amyloidosis, with a median survival being less than 6 months at the stage of congestive heart failure.<sup>10</sup> In recent series, 3-years survival was approximately 80% and median survival time ranged from 26 to 56 months in patients with AL amyloidosis treated with cardiac transplantation plus ASCT-high-dose melphalan or melphalan-prednisone,<sup>11-13</sup> a rate being comparable to those of cardiac transplantation for other indications.

In conclusion, we present the first case of bilateral kidney infarcts due to AL amyloidosis associated with prominent massive renal vascular amyloid deposits. This patient received chemotherapy and heart transplant and 40 months later, he is doing very well, which illustrates the huge progress made in the treatment of systemic AL amyloidosis.



**FIGURE 2.** (A) Amorphous, green, hyaline material replacing, and expanding the normal vessel wall with partial occlusion of the lumina. Note apparent lack of glomerular involvement (original magnification  $\times 100$ ). Inset: Apple green birefringence of arteriole wall under polarized light after staining with Congo red (original magnification  $\times 200$ ). (B) Direct immunofluorescence typing with anti-light chain antibodies. Note bright staining of arterioles (arrows) with lambda light chain antibody and negative stain for kappa light chain (original magnification  $\times 100$ ). (C) Electron microscopy revealed amyloid deposition in glomerulus at the endothelial side of the glomerular basement membrane (arrow) (original magnification  $\times 10000$ ), with a fibrillary appearance on higher magnification (inset, original magnification  $\times 100000$ ). (D) Amorphous red material expanding the epicardial vein. The deposits are positive with Congo red (inset myocardial wall) (original magnification  $\times 200$ ).

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