

Cardiac amyloidosis: a challenging diagnosis

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ABSTRACT

Cardiovascular involvement of amyloidosis is present in 90% of cases, which is frequently associated with the primary form of the disease (AL amyloidosis). Clinical manifestations are represented by heart failure due to restrictive cardiomyopathy and electrical impulse conduction abnormalities, which are clinically remarkable in up to 50% of the cases. The prognosis of patients with systemic amyloidosis is directly associated with the presence of cardiac involvement, such that survival does not usually exceed 4 months after the onset of heart failure signs and symptoms. The authors report a case of primary systemic amyloidosis, diagnosed only at autopsy, with severe cardiac involvement.

Keywords

Amyloidosis; Cardiomyopathy, Restrictive; Autopsy.

INTRODUCTION

Amyloidosis comprises a group of disorders that share, in common, the interstitial deposition of insoluble fibril protein, called amyloid, which exhibits particular physicochemical and staining properties. This substance may be identified by different histochemical methods such as the Congo red dye that produces an apple-green birefringence on stained sections under polarized light.

The amyloid deposition may be organ-specific or multisystemic. Infiltrated tissue exhibits damaged function by compression and atrophy of the interstitial cells. Cardiac amyloidosis is the most common infiltrative cardiomyopathy.¹

Two types of amyloid commonly infiltrate the heart: a) immunoglobulin light-chain (AL or primary systemic) amyloid, and b) transthyretin (TTR) amyloid.² Cardiac involvement in amyloidosis is commonly associated

with the primary form of the disease (AL amyloidosis), which is related to the deposition of monoclonal light chain immunoglobulin.³ In this type of amyloidosis, the heart is involved in 90% of the cases and 50% of them present remarkable clinical manifestations. The prognosis of these patients is directly associated with the presence of cardiac involvement. The overall survival time drops from 13 months to 4 months when the signs and symptoms of heart failure ensue.²⁻⁵

ATTR progresses more slowly than AL amyloidosis, and most untreated patients live many years after the first signs of the disease.²

Diastolic cardiac failure and conduction system disturbances characterize the cardiac involvement. The commonest congestive signs are represented by dyspnea and edema of lower extremities. Coronary artery amyloid deposition may lead to angina or

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myocardial infarction. The presence of syncope may be related to autonomic dysfunction and/or arrhythmias, which usually signals a poor prognosis since it may lead to sudden death. The amyloid deposition in the cardiac conduction system frequently involves the His-Purkinje system, while the atrioventricular node function is usually spared and preserved.^{5,6} The predominant valvar involvement in amyloidosis is very uncommon.^{7,8}

The clinical diagnosis of cardiac involvement in amyloidosis is challenging. Suspicion should be raised on the basis of clinical features and non-invasive examination techniques, like the presence of low-voltage QRS complex on ECG and thickening of the ventricular wall on echocardiography. Cardiac magnetic resonance imaging and the positron emission tomography scan are more specific and therefore may be useful. The gold standard diagnostic tool is the presence of amyloid in endomyocardial or abdominal fat biopsy.⁶

Treatment of cardiac amyloidosis is based on the relief of symptoms and, when feasible, in the reduction of the amyloid production with the aid of chemotherapy or bone marrow transplantation.^{4,6}

CASE REPORT

A 46-year-old male patient sought the emergency room complaining of abdominal pain, nausea, vomiting, anorexia, drowsiness, and coughing when

lying down. His past medical history included non-dialytic chronic renal failure of unknown cause, and aortic valve insufficiency. During the last 40 days he referred weight loss of 15 kg.

On admission he was pale, dehydrated, and icteric; his pulse rate was 100 beats per minutes, and his respiratory rate was 16 breaths per minute. The cardiac and abdominal examination was unremarkable but the pulmonary examination revealed reduced breath sounds in the lung bases.

Laboratory work-up showed persistent and elevated liver enzymes, bilirubin, prothrombin activity, and creatinine as summarized in Table 1. Antinuclear antibody, VDRL, hepatitis A, B and C, cytomegalovirus, rubella, and toxoplasmosis serologies were negative.

The plain chest radiography (Figure 1) showed a reduced costophrenic recess and an enlarged cardiac silhouette.

The electrocardiogram showed narrow QRS supraventricular tachycardia, low voltage QRS complexes in the frontal leads, and electrically inactive areas in the inferior and anterior left ventricular walls (Figure 2). Abdominal ultrasonography evidenced loss of renal corticomedullary differentiation while the remaining viscera and the abdominal cavity were within normal limits.

The patient outcome was unfavorable with decreased mental status and progressive dyspnea requiring orotracheal intubation and mechanical

Table 1. Laboratory analysis during hospitalization

	1st day	2nd day	3rd day	4th day	5th day	RV
TB	2.9	3.2	3.7	4.5	4.1	0.3-1.2 mg/dL
DB	1.9	2.1	2.5	2.8	2.3	< 0.2 mg/dL
AP	264	244	-	-	-	90-360 U/L
γGT	116	105	79	-	-	< 73 U/L
AST	223	218	141	113	53	0-33 U/L
ALT	1562	1452	935	816	380	10-40 U/L
INR	1.45	1.2	1.96	2.21	2.08	1
LDH	-	-	466	-	-	240-480 U/L
C-RP	-	-	8.9	8.9	-	1 mg/dL
TP	-	-	-	4.9	4.4	5.7-8.2 g/dL
C	2.7	2.6	2.6	3.0	3.0	0.6-1.3 mg/dL
U	117		101	109	77	20-40 mg/dL

ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, C = creatinine, C-RP = C-reactive protein, DB = direct bilirubin, γGT = gamma glutamyl transpeptidase, INR = international normalized ratio, LDH = lactate dehydrogenase, RV = reference value, TB = total bilirubin, TP = total protein, U = urea.

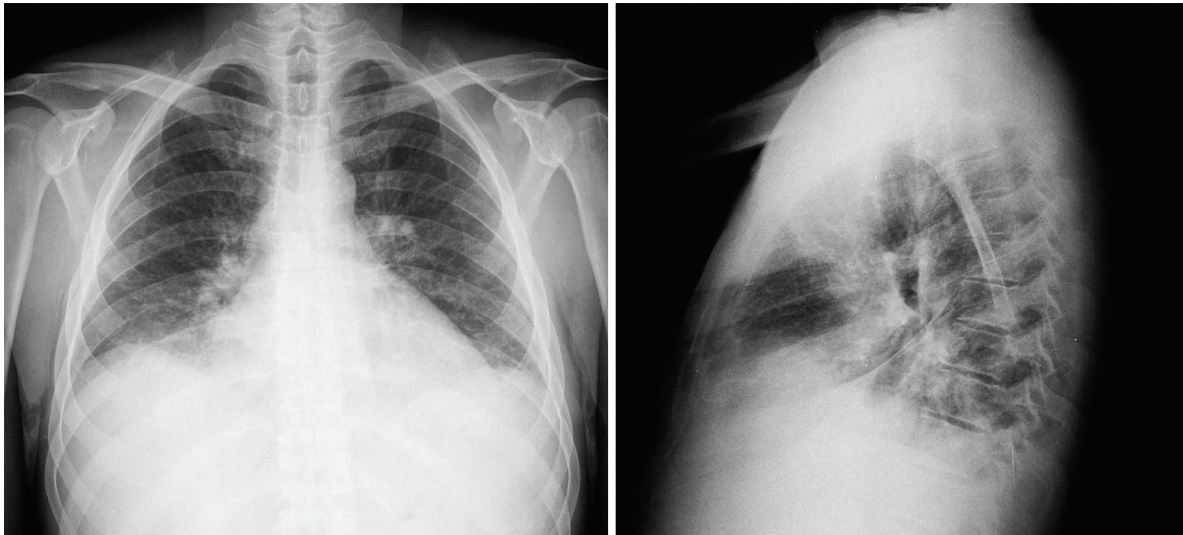


Figure 1. Plain chest radiography showing cardiomegaly and left reduced costophrenic recess.

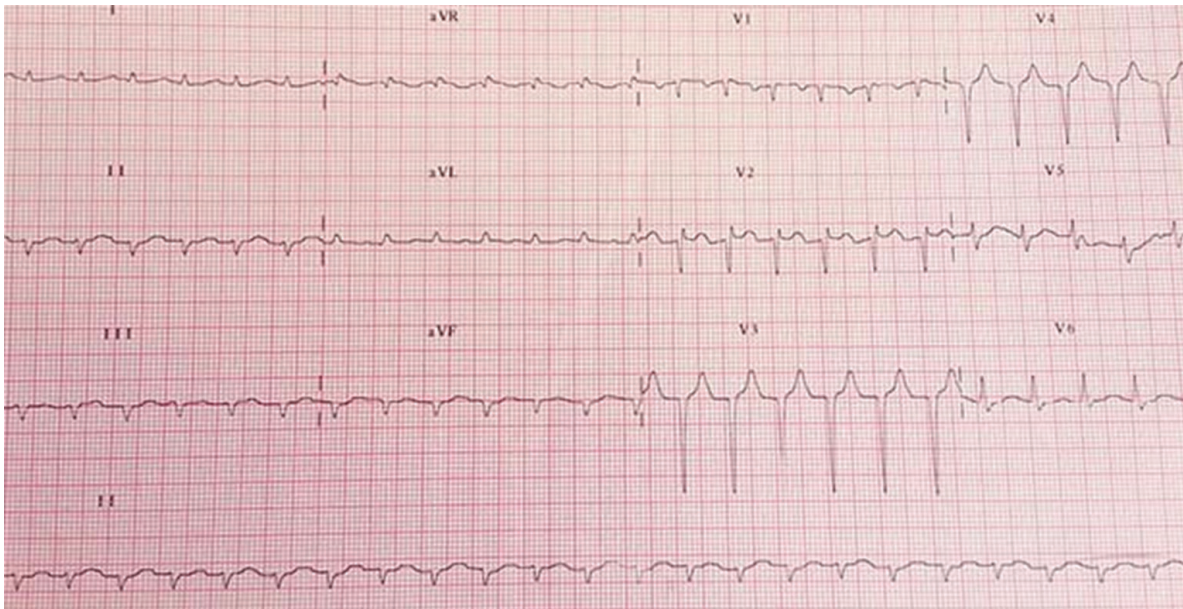


Figure 2. Electrocardiogram showing narrow QRS supraventricular tachycardia, and low voltage QRS complexes on frontal leads and anterior left ventricular walls.

ventilatory support. He presented two episodes of cardiac arrest ending with unresponsive hypotension and death. Because of the impossibility to assure the diagnosis during life, an autopsy was undertaken.

AUTOPSY FINDINGS

At ectoscopy, generalized edema was present. At the opening of cavities, 1400 mL was drained from the right hemithorax, 1200 mL from the left hemithorax, 50 mL from the pericardial sac, and 1200 mL from the peritoneal cavity. All effusions were clear and yellowish.

The brain weighted 1250g (reference value [RV]: 1100 g) and presented a slight edema characterized by broadening of gyri and sulci effacement. On brain microscopy, vascular congestion was observed.

The heart weighted 580 g, (RV: 350 g) and presented thickening of ventricular walls measuring 1,6cm (RV: 1,5cm) (Figure 3A). Ventricular cavities were dilated and a mural thrombus was identified in the right atrium. The endocardium showed a diffuse micro granular surface accompanied by thickening and retraction of the aortic valve (Figure 3B and 3D). Histologic examination revealed the interstitial deposition of amyloid surrounding the cardiomyocytes

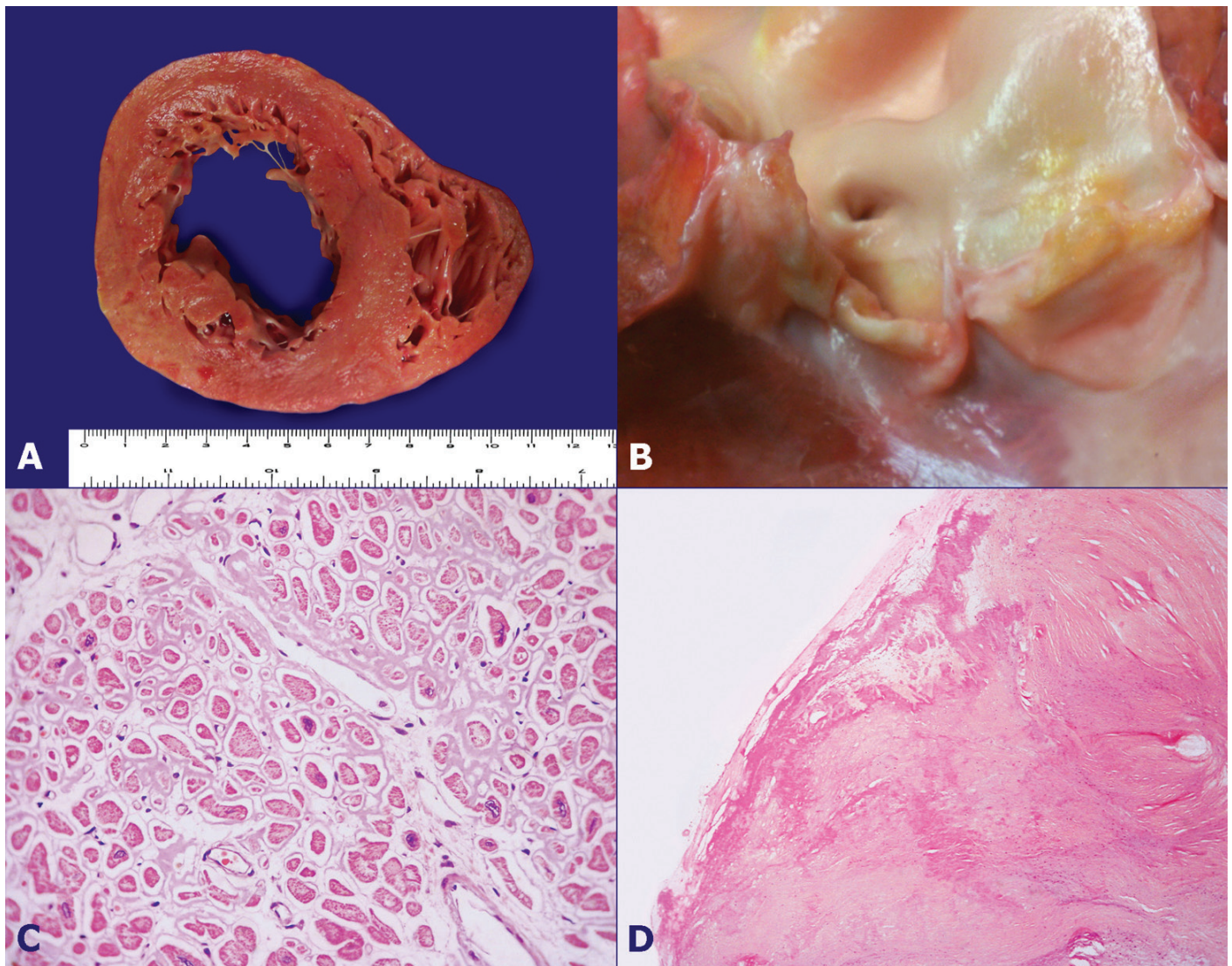


Figure 3. **A** – Transversal section of the ventricles showing the myocardial thickening associated with the left ventricular dilatation; **B** – Thickened and retracted aortic valve; **C** – Photomicrography of the myocardium showing interstitial deposition of the amyloid substance involving the myocardiocytes (HE – AO = 200X); **D** – Photomicrography of the aortic valve showing amyloid substance deposition (HE – AO = 100X).

and thickening of the ventricular wall and endocardium (Figure 3C).

The right lung weighed 950 g and the left 640 g (RV: 450 g and 400 g, respectively); both were congested. Hemorrhagic infarctions were identified in the right lower and middle pulmonary lobes (Figure 4A). On histology, besides the findings consistent with pulmonary infarction (Figure 4B), alveolar septa (Figure 4C and 4D) and vessel walls (Figure 4D) were thickened by amyloid deposition. Alveolar edema and hemosiderin-laden macrophages (heart failure cells) characterized the microscopic findings.

The liver weighed 1680 g (RV: 1400 g) and exhibited the classic nutmeg appearance (Figure 5A).

Hemorrhagic necrosis of the zone 3 and hemosiderin were present on histology (Figure 5B). Hepatic amyloidosis involvement was restricted to the portal vessel wall (Figure 5C).

The spleen weighed 450 g (RV: 200 g) was hardened and pale. On microscopy, the amyloid was diffusely deposited involving both the white and the red pulp (Figure 5D).

The kidneys weighed 150 g each (RV: 200 g) and showed a granular external surface (Figure 6A). The parenchyma was atrophic with hilar fat replacement (Figure 6A). Amyloid deposition was observed in some glomeruli, widening the mesangium (Figure 6B) and thickening the afferent arteriole accompanied by

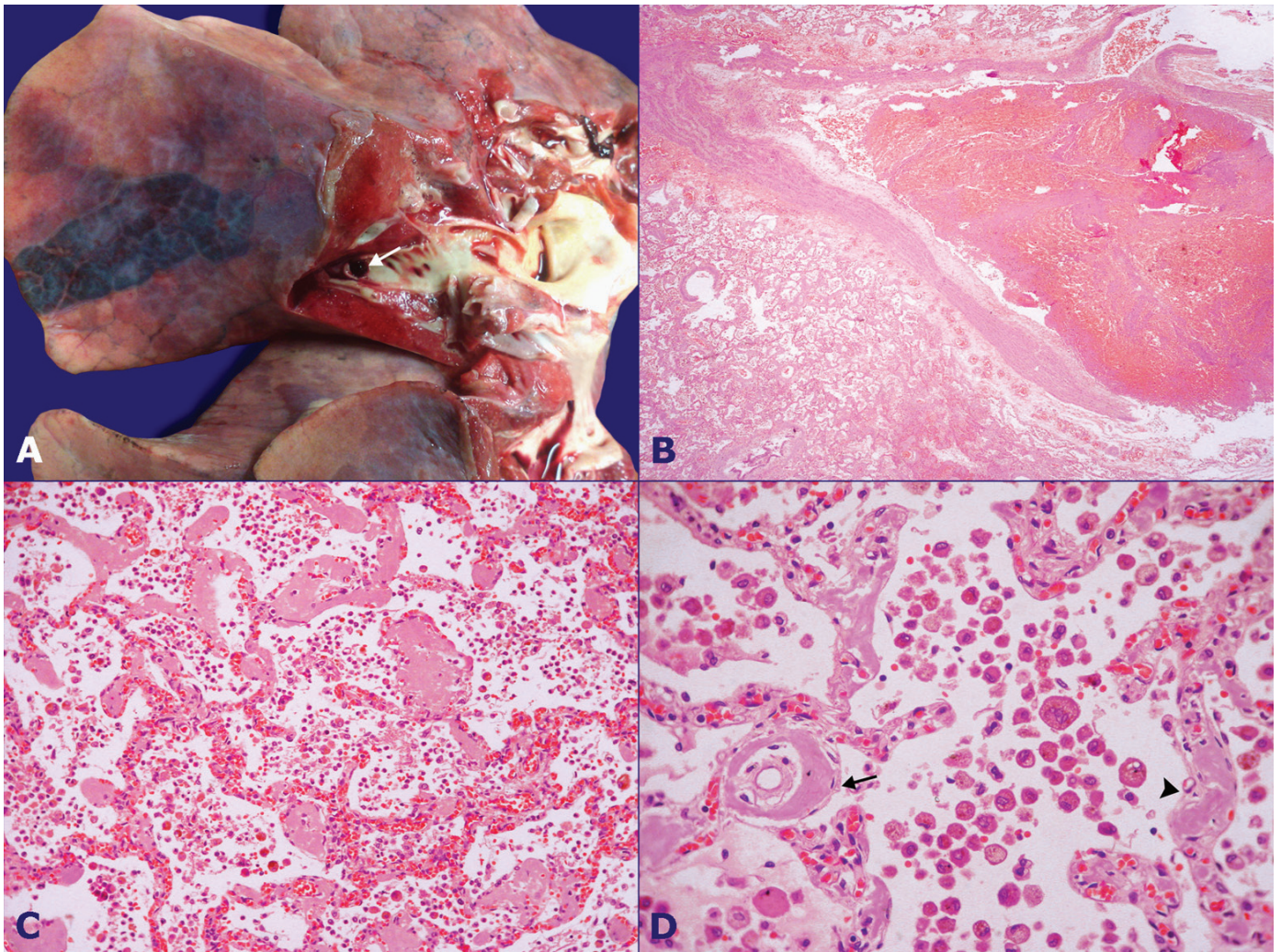


Figure 4. **A** – Pulmonary hemorrhagic infarct associated with the pulmonary embolus found in the hilum (white arrow); **B** – Photomicrography of the pulmonary vessel showing evidence of the pulmonary embolus with the hemorrhagic area of the parenchyma (HE – AO = 50X); **C** – Photomicrography of the lung showing diffuse thickening of the interalveolar septa (HE – AO = 200X); **D** – Photomicrography of the lung showing diffuse thickening of the interalveolar septa (arrowhead) and of the vascular walls (arrow) due to deposition of amyloid substance and the presence of macrophages with hemosiderin pigment in the alveolar spaces (HE – AO = 400X).

glomerular atrophy (Figure 6C and 6D). Scattered areas of fibrosis and lymphocytic infiltration were observed.

Vascular wall deposition of amyloid was also observed in the thyroid, pancreas, and small bowel, where hemorrhagic foci were observed. The Congo red staining after examination under polarized light microscopy confirmed amyloid deposition (Figure 7A and 7B).

Signs of infection, chronic inflammatory disease, or plasma cell neoplasm were not identified. Bone marrow biopsy was not performed.

Immunohistochemical staining was performed for serum amyloid A and monoclonal lambda and kappa light-chains (ATTR wild-type was not available). The

reaction was positive for monoclonal lambda light-chain on vascular walls and interstitial amyloid deposits (Figure 7C and 7D).

DISCUSSION

In the present case, the autopsy was fundamental to establish the diagnosis. Systemic amyloidosis is frequently associated with plasma cell dyscrasia, chronic inflammatory disease, chronic infection and hemodialysis. The two most common types of amyloid that infiltrate the heart are: immunoglobulin light-chain (AL or primary systemic) amyloid, and transthyretin (TTR) amyloid. AL amyloidosis has a poor prognosis,

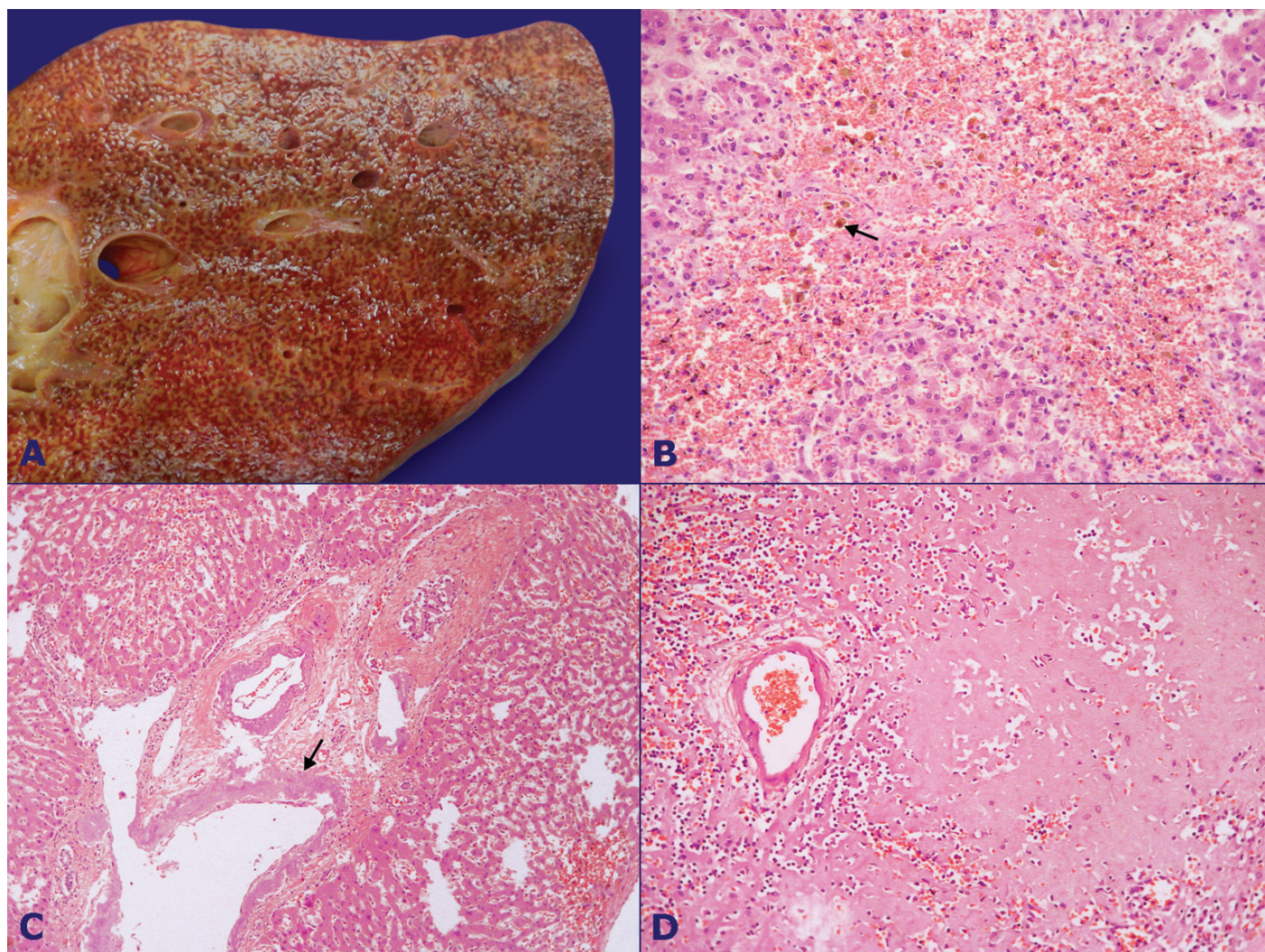


Figure 5. **A** – Liver segment showing the classical aspect of “nutmeg liver”; **B** – Photomicrography of the liver showing centrilobular hemorrhagic necrosis associated with the deposition of hemosiderin (arrow) (HE – AO = 400X); **C** – Photomicrography of the liver involvement by amyloidosis restricted to the portal vascular structures (arrow) (HE – AO = 100X); **D** – Photomicrography of the spleen showing the extent involvement of the spleen by amyloidosis, both in the red and the white pulps (HE – AO = 400X).

as in this case, with median survival following diagnosis of < 1 year in the presence of heart failure symptoms. Unlike AL heart disease, transthyretin-related amyloid cardiomyopathy is slowly progressive and clinically well tolerated, often defying diagnosis until marked ventricular wall thickening, profound diastolic dysfunction, and conduction disease have occurred. Untreated, survival with transthyretin-related cardiac amyloidosis is measured in years to decades.⁹ Most of the AL-amyloidosis cases are not associated with multiple myeloma or other B-cell neoplasia, and are traditionally classified as primary amyloidosis.

In the case presented herein, the initial presentation was renal failure. The involvement of other organs is

generally silent and progressive. Cardiac involvement, in this form of amyloidosis, shows a restrictive pattern with elevated jugular venous pressure, ventricular gallop, systemic venous congestion, and hepatomegaly.¹ The outcome is variable among different types of amyloidosis, but the cardiac involvement defines the prognosis in all types.¹⁰

Cardiac involvement is represented by the thickening of all cardiac chamber walls accompanied by biatrial dilation, a normal or mildly dilated right ventricle, and a normal-to-small left ventricle chamber.¹⁰ In our case, we observed left ventricle dilation, which was most probably related to the aortic insufficiency that was secondary to the valvar amyloid infiltration.

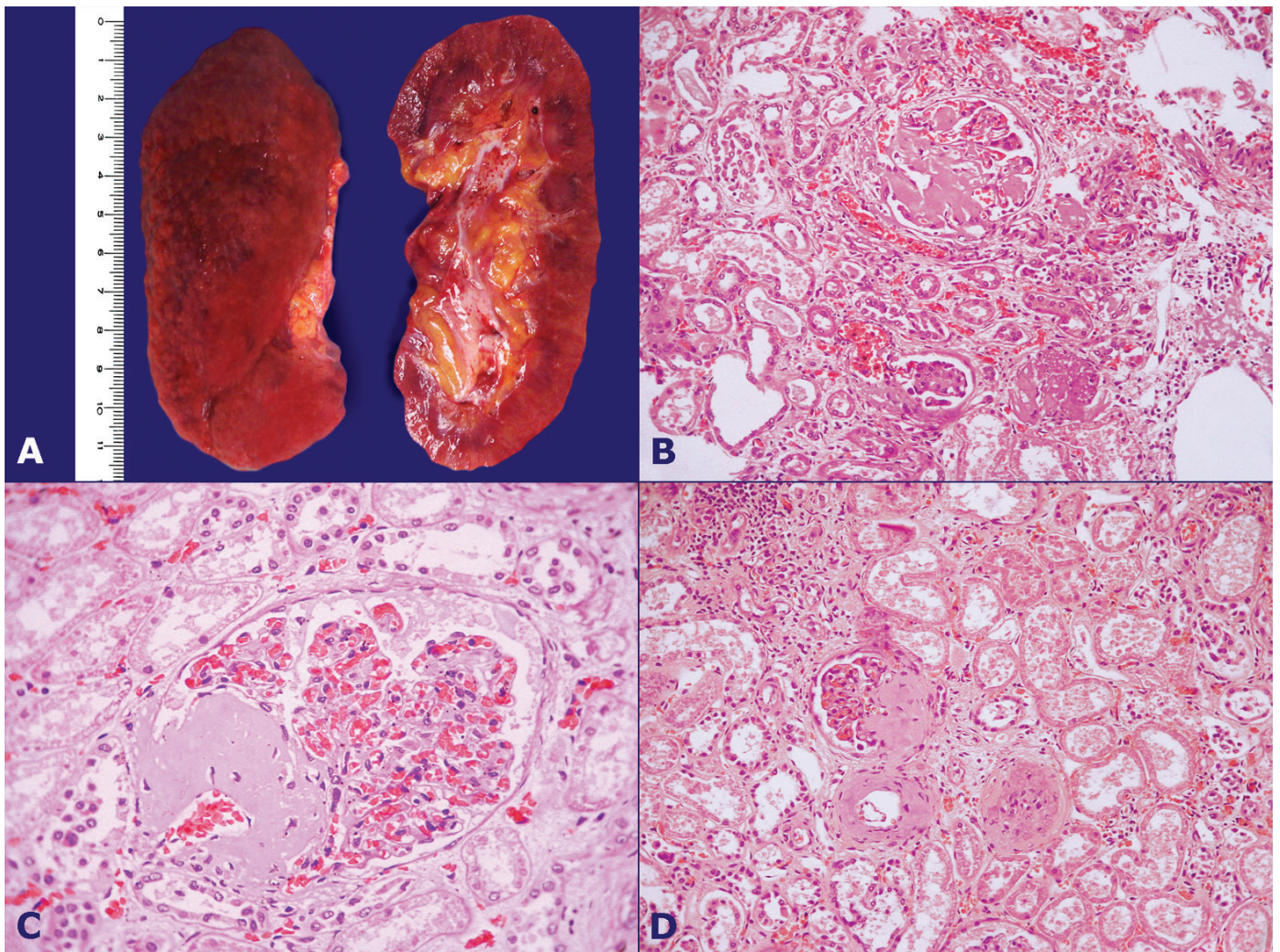


Figure 6. **A** – Gross appearance of the contracted kidneys, with atrophy and granulous surface; **B** – Photomicrography showing mesangial deposition of amyloid substance (HE – AO = 200X); **C** and **D** – Photomicrography of the kidney showing (in the great majority of the glomeruli) the evident thickening of the afferent arteriole (C: HE – AO = 400X; D: HE – AO = 200X).

Pulmonary amyloidosis is rare; however, this involvement is more frequently observed in primary AL amyloidosis. In these cases, the amyloid is deposited in the airways or in the alveolar septa following either a diffuse or nodular deposition pattern. In our case, the autopsy findings showed parenchymal and vascular amyloid deposition in a diffuse pattern, which corresponded to the most common pattern of systemic amyloidosis.¹¹

The glomerular mesangial expansion is the most frequent renal involvement in amyloidosis. In our case, we observed the predominance of vascular involvement with consequent parenchymal atrophy, which is more rare.^{12,13}

Immunohistochemical staining for monoclonal lambda light chain was positive in this case. This may

suggest primary amyloidosis, which may be related to some plasma cell dyscrasia. Unfortunately the bone marrow was not sampled in this autopsy, but bone lesions and systemic signs of plasma cell proliferation were absent.

We would like to highlight the marked elevation of hepatic enzymes, which were somewhat disproportional to the liver parenchyma lesion. We considered that the passive hepatic congestion added to the amyloid deposition in hepatic vessel walls could lead to hepatocytes ischemia and, consequently, an increase in hepatic enzymes.¹⁴⁻¹⁶ Recently, a study involving 489 patients diagnosed with heart failure (independently of the staging) evidenced elevated determination of transaminases in 25% of patients.¹⁷ Passive hepatic congestion due to increased central venous pressure

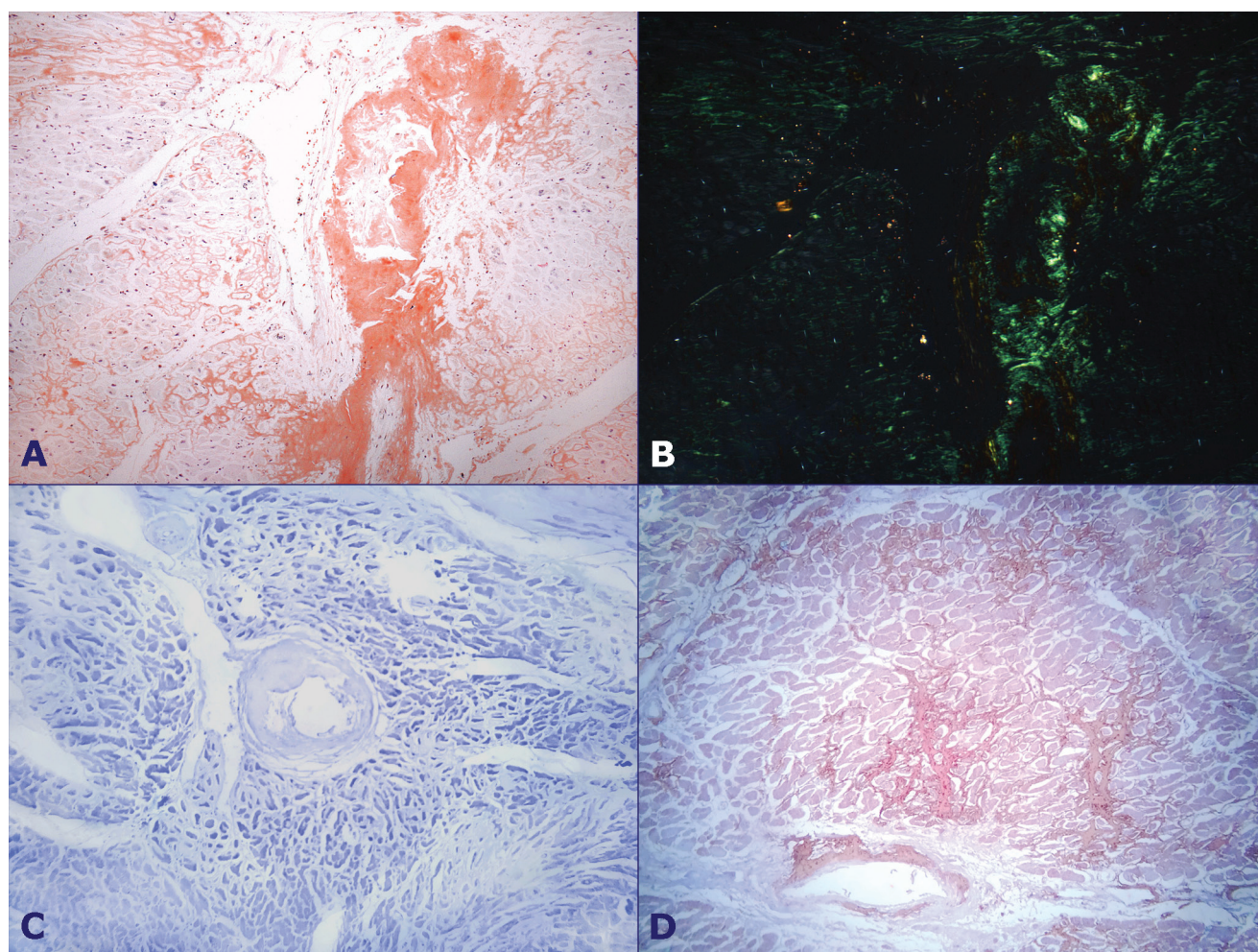


Figure 7. Photomicrography of the cardiac tissue showing in **A** deposition of amyloid stained by the Congo red (100X) and in **B** the same slice under polarized light microscopy showing the apple green color (100X). Immunohistochemical staining negative for kappa light-chain in **C** ([Monoclonal Kappa Light Chain antibody - Dako, USA, 1:1000], 100X) and positive for lambda light-chain in **D** ([Monoclonal Lambda Light Chain antibody - Dako, USA, 1:1000], 100X).

may cause elevations of liver enzymes and both direct and indirect serum bilirubin. Impaired perfusion from decreased cardiac output may be associated with acute hepatocellular necrosis with marked elevations in serum aminotransferases.¹⁸ This entity was called ischemic hepatitis. Cardiogenic ischemic hepatitis (“shock liver”) may ensue following an episode of profound hypotension in patients with acute heart failure. Hepatic dysfunction due to passive congestion is particularly common in patients with right-sided heart failure with elevated right ventricular pressure, which occurs in restrictive cardiomyopathy and was seen in this case.

Cardiac amyloidosis diagnosis is difficult, and often diagnosed solely at autopsy. Therefore, an early diagnosis is fundamental for starting the treatment as soon as possible, since it may be the only chance for a good prognosis.

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