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Isolated amyloidosis of the atrioventricular valves

A study of one case, curiously associated with diffuse storage of plant wax paraffin

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Summary. Autopsy of a 55-year-old man, whose death was due to coronary failure, revealed: 1) localized amyloidosis limited to the leaflets of the atrioventricular valves and their chordae tendinae, with no apparent relationship to atherosclerosis, and 2) deposits of crystallized vegetable hydrocarbons of dietary origin, mainly in the lungs, lymph nodes and liver.

Observations of isolated amyloidosis in healthy valves are exceptional. The association with multiorgan deposition of vegetable wax hydrocarbons raises the question of a possible link between these two entities.

Key words: Alkane storage disease – Amyloidosis of the heart valves – Heart valve diseases

Introduction

We wish to report the case of a subject presenting isolated amyloidosis of the atrioventricular valves, with no pre-existing sclerocalcific lesions. This exceptional observation raises questions which are difficult to answer.

Case report

A 55-year-old farmer was admitted to Rangueil Hospital, Toulouse, for unstable angina of recent appearance. The risk factors were hypertension treated by methyldopa* and a tobacco consumption of one packet of cigarettes per day. The electrocardiogram showed subendocardial ischaemia which yielded to medical treatment. Coronarography showed non-threatening stenosis. Neither T-mode dimensional echographic studies nor left ventriculography showed any morphological or functional anomaly. The thoracic x-ray, however, showed a miliary appearance, but there were no respiratory functional symptoms. Standard biological tests showed no particular anomaly; the ESR was 7 mm at 1 h and blood protein electrophoresis was normal. The subject died suddenly of ventricular fibrillation and an autopsy was carried out.

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Autopsy findings. The external aspect of the heart (420 g) was normal. On incision, the left ventricular wall was of normal thickness and cut sections showed no anomaly. The leaflets of the mitral and tricuspid valves appeared thickened, of beige-orange colour and slightly translucid; the surface was smooth and of supple consistency. The chordae tendinae were not disrupted. The sigmoid valves were normal, the surface of the atrial and ventricular endocardium showed no alteration. The coronaries showed scattered calcific stenosis without thrombosis.

After fixing in formalin, the atrioventricular valves showed a more irregular appearance, with rounded swellings on the surface; their chordae tendinae presented numerous nodules giving a moniliform appearance (Fig. 1).

The other organs presented no particular lesion on gross examination, with the exception of the lungs, which contained whitish micronodules predominately in the upper lobes.

Materials and methods

The heart was fixed en bloc in 10% neutral buffered formalin, as were specimens of most organs: lungs, liver, spleen, mediastinal and abdominal lymph nodes, kidneys, adrenal glands, bladder, prostate, aorta, brain and skin.

Routine staining with hematoxylin-eosin-saffron and congo red was performed on all specimens with incubation with potassium permanganate according to Wright's technique (Wright et al. 1977) which is derived from the Romhanyi trypsin technique (Romhanyi 1972). After embedding in araldite semithin sections were cut to 1 μ and stained with toluidine blue. A formalin-fixed sample of the mitral valve was embedded in araldite and cut to 1,000 Å. The grills were stained with uranyl acetate-lead citrate and examined using a Hitachi H 300 transmission electron microscope.

Results

Microscopic examination of the atrioventricular valves and their chordae tendinae showed multiple

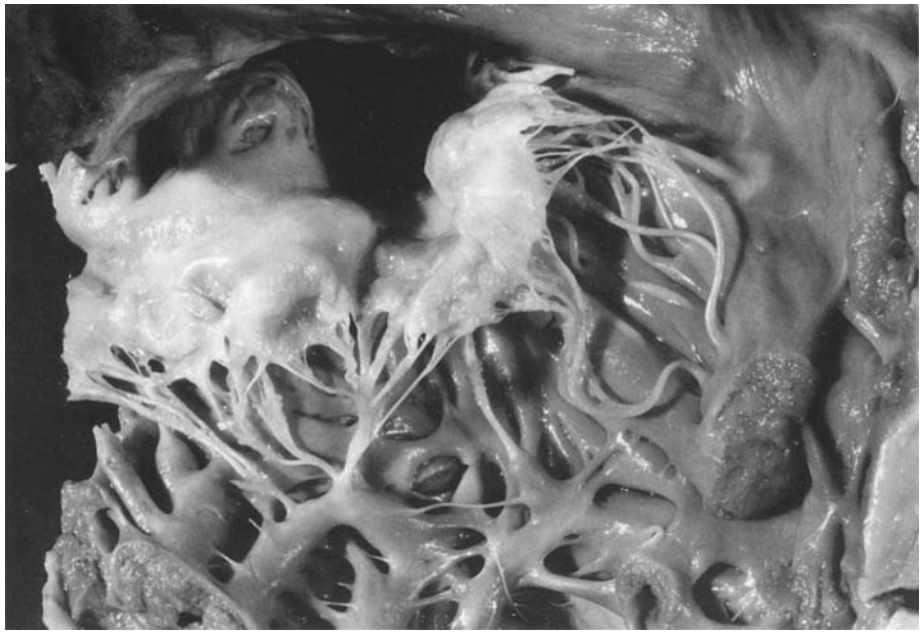

Fig. 1. Gross appearance of the mitral valve after formalin fixation: the leaflets are thickened, their surface presents rounded swellings and the chordae tendinae show numerous spicules

nodules of varying size separating the collagen bundles of the pars fibrosa and raising the endocardium (Fig. 2). These nodules, eosinophilic and homogeneous, resembled amyloid deposition. This was confirmed by staining with congo red, with subsequent demonstration of green dichroism (this stain resists permanganate), and by ultrastructural examination. The latter method showed tangled microfilaments 10 nm in diameter, in large patches, isolating the collagen bundles and associated with rare fibroblastic cells (Fig. 3). The remainder of the valvular tissue showed no inflammatory or cicatricial lesion, no calcification or fibrinoid or myxoid degeneration.

There was no interstitial or perivascular amyloid deposit in the auricular and ventricular myocardium. The sigmoid valves were normal. The coronary arteries showed areas of stenosis, without thrombosis.

In the lungs giant-cell granulomas of foreign body type were found surrounding crystals of a fatty substance; these granulomas were dispersed in the subpleural and peribronchovascular tissues (Fig. 4A).

Numerous crystals were also observed in the abdominal lymph nodes (Fig. 4B) and to a lesser extent in the liver, spleen, adrenals and mediastinal lymph nodes.

Congo red staining was used to detect amyloidosis in organs other than the heart, but was negative in all specimens.

Biochemical examination. The fact that the whole heart was formalin-fixed made it impossible to isolate and identify the proteinaceous fibrils composing the valvular amyloid deposits.

The crystallized fatty substance observed in the lungs and in the subdiaphragmatic organs was identified by mass spectrometry: it was composed of n-alkanes, saturated straight-chain hydrocarbons with 29 C-atoms, and to a lesser extent, with 31 C-atoms.

Discussion

The valves may be affected by amyloid deposition in four types of amyloidosis: generalized amyloidosis, familial amyloidosis, cardiac amyloidosis, and isolated valvular amyloidosis.

In generalized amyloidosis of AL type (primary and associated with plasma cell dyscrasia), the myocardial deposits are interstitial and perivascular (Störkel et al. 1983). The valves are often affected, principally the atrioventricular valves: tricuspid 90%, mitral 86%, pulmonary 57% and aortic 33% (Smith et al. 1984). These valves may be extensively infiltrated: several studies report massive involvement of the valves in cases of primary systemic amyloidosis (Koletsky and Stecher 1939; Lindsay 1946; Garcia and Saeed 1968).

However, in AA type generalized amyloidosis, the deposits are perivascular and do not seem to be accompanied by endocardiac and valvular infiltration.

The heart is involved in two types of familial amyloidosis: in familial amyloidosis with polyneuropathy (Eriksson et al. 1984) and in familial amyloidosis with severe amyloid heart disease

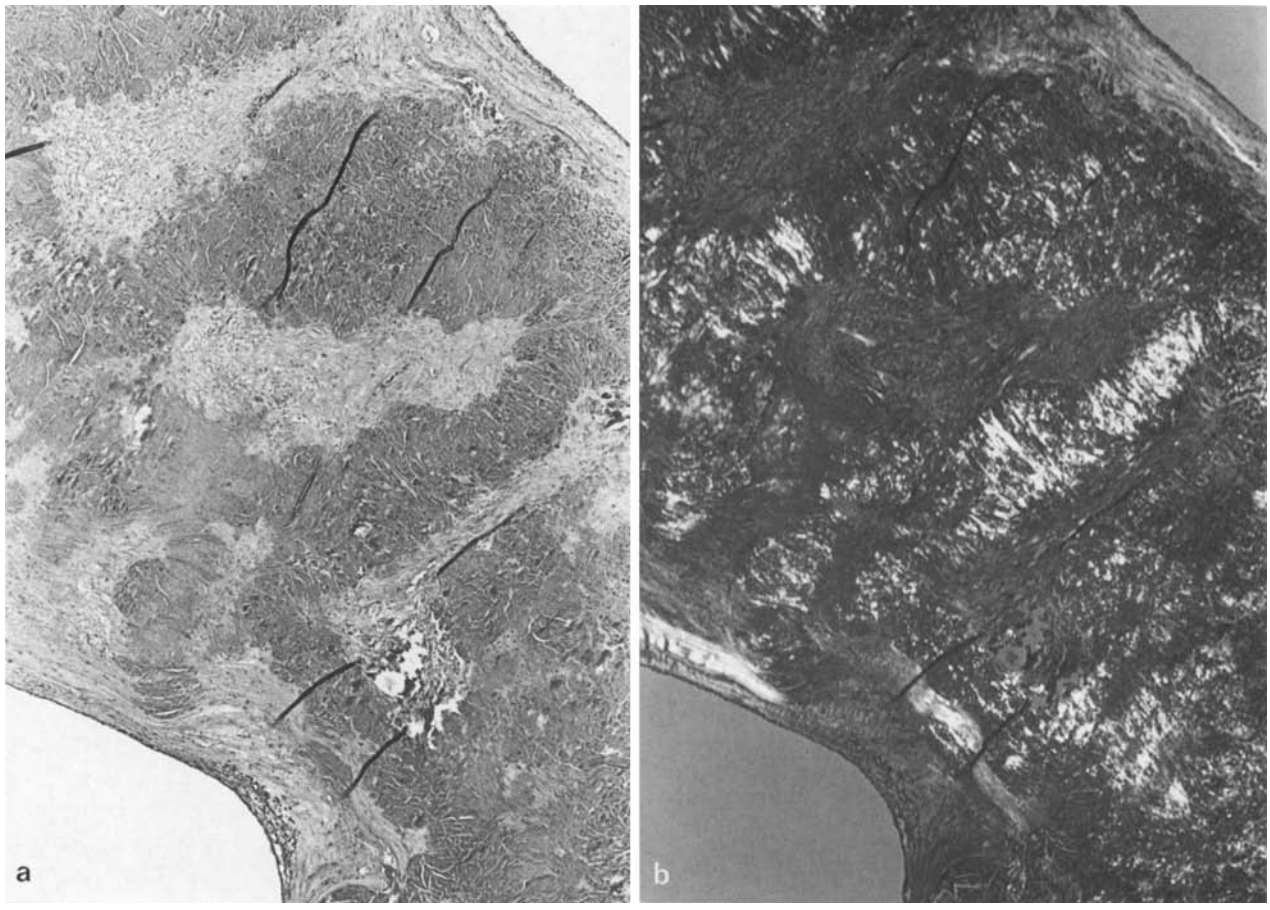

Fig. 2a, b. The valvular leaflets contain numerous nodules, staining with congo red, separating the collagen bundles of the pars fibrosa. Coloration and birefringence are still evident after incubation with potassium permanganate. (Potassium permanganate, congo red ×40)

Fig. 3. Electron microscopy shows a characteristic tangle of 10 nm fibrils together with some collagen bundles in the valvular leaflets. (Transmission electron microscopy, ×13,000)

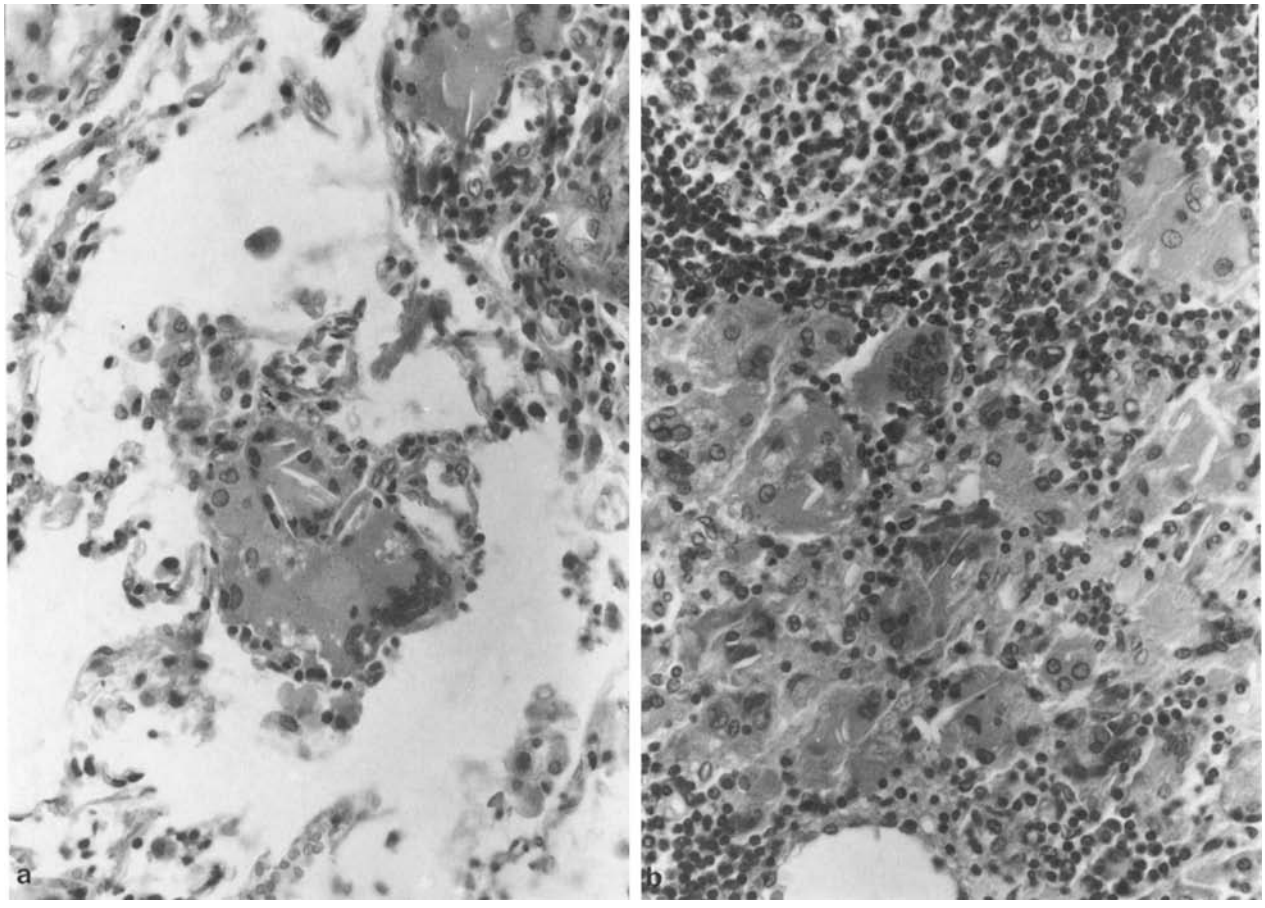

Fig. 4a. Cluster of giant cells containing fatty body crystals and asteroid bodies, in an alveolar septum, near a bronchovascular bundle. (Hematoxylin-eosin-saffron, ×250). **b** Aggregate of crystal-containing giant cells, in a retroperitoneal lymph node along the abdominal aorta, in contact with a germinative centre. (Hematoxylin-eosin-saffron, ×250)

(Frederiksen et al. 1962); in the latter type the valves are affected.

In senile cardiac amyloidosis (SCA), amyloid deposits in the myocardium are interstitial and perivascular. Valvular involvement is less frequent than in generalized AL type amyloidosis, but once again the atrioventricular valves are the most commonly affected: tricuspid 15%, mitral 38%, pulmonary 8% and aortic 15% (Smith et al. 1984).

Isolated atrial amyloidosis (IAA) has been more recently described as a distinct entity (Westermark et al. 1979; Looi 1981). Deposition is limited to the interstitium of the atrial walls and the interatrial septum. The frequency of valvular involvement is unknown. This isolated atrial amyloidosis is distinguished from senile amyloidosis by its localization and by the absence of protein Asca (Westermark et al. 1979)

Amyloidosis restricted to the valves alone is found in 15,5% of sclerocalcific valves, in the form of small deposits in close proximity to calcified areas (Goffin 1980, Ladefoged et al. 1984); they are permanganate-resistant. More recently, amyloid deposits have been reported in porcine bioprosthetic cardiac valves (Goffin 1984). Lastly, extremely rare cases of isolated valvular amyloidosis occurring in noncalcific valves have been reported (Pomerance 1977); in one case deposition involved the pulmonary and tricuspid valves and was associated with a duodenal carcinoid tumour (Jakobovitz and Dustin 1974).

In our observation, the amyloid was deposited in the form of large nodules in the valvular tissue and the chordae tendinae of the atrioventricular valves. The nodules were interspersed between the collagen bundles of the valvular tissue, but there was no cicatricial lesion nor dystrophic calcification. No amyloid deposit was observed in the remainder of the heart, nor in any of the autopsy samples, in particular liver, spleen, kidneys, adrenals, aorta, brain, skin. Congo red staining resisted potassium permanganate, which excluded AA type amyloidosis (Romhanyi 1972; Wright et al. 1977).

Our case thus forms part of the group of excep-

tional isolated valvular amyloidosis in a healthy valve. The fact that deposition was restricted to the leaflets and chordae tendinae of the atrioventricular valves, with no cicatricial lesion, raises the following question: does the tissue of the pars fibrosa have a particular composition which would account for this preferential localization?

This valvular amyloidosis had no effect on haemodynamics nor on atrioventricular conduction (normal PR interval on the ECG). In spite of the absence of microscopical infarction lesions, the death of the subject due to ventricular fibrillation was attributed to the coronary stenosis.

Moreover, the valvular amyloid deposit was associated with an overload of straight-chain saturated hydrocarbons with 29 and 31 C-atoms. These two n-alkanes are particularly well represented in the plant kingdom in epicuticle wax and are abundant in apple peel. The case history revealed excessive consumption of apples, to which the hydrocarbon overload was attributed. As far as we know, such an overload has never been described: it is discussed in a separate work (Duboucher et al. 1986). Although there is no obvious relation between these two exceptional entities (isolated amyloidosis of the atrioventricular valves and vegetal alkane storage), their association is certainly not fortuitous. The indirect relation which undoubtedly exists remains to be clarified.

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