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Clinical Case Report

Transthyretin-related amyloid in a saphenous vein. Histological diagnosis in a patient undergoing coronary artery bypass surgery☆

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ABSTRACT

Amyloidosis is an underdiagnosed and challenging disease with clinical and etiologic heterogenicity, requiring amyloid subtyping because of the distinctive prognostic and therapeutic impact. Transthyretin amyloidosis is more common in elderly patients, and in such population undergoing cardiovascular surgery, it could be worthy to be investigated. We herein describe an unusual case of transthyretin-related vascular amyloidosis in an 81-year-old man undergoing coronary artery bypass surgery. Diagnosis done after histology showed an intimal eccentric thickening in a remnant segment of the right saphenous vein that was harvested for grafting. Transthyretin-related amyloidosis was demonstrated by histochemical Congo Red staining under polarized light and by immunohistochemistry, corresponding to the intimal thickening. The thorough histological analysis was crucial for the diagnosis of a previously unknown transthyretin-related vascular amyloidosis.

1. Introduction

Amyloidosis represents a clinically and etiologically heterogeneous disease due to an altered protein folding that causes the extracellular deposition of insoluble polymers with a peculiar (beta-sheet) spatial organization [1]. Amyloid progressively accumulates in various tissues, including cardiovascular and nervous structures with consequent functional impairment [2]. By using Congo Red histochemical staining on histological sections, amyloid is revealed as apple green deposits under polarized light [3]. Three main types of amyloidosis are known, depending upon the altered polymerizing protein [2]. Immunoglobulin light chain amyloidosis (AL) is the most frequent type; it is related to abnormal Ig light chain production by a clonal population of bone-marrow-derived plasma cells, as in multiple myeloma. Transthyretin-related amyloidosis (ATTR) is the second form of cardiac amyloidosis, due to the deposition of the transport protein transthyretin that can be altered because of a genetic mutation or occur as wild-type (not mutated) form strongly related to aging and formerly known as "senile cardiac amyloidosis" [3]. Finally, serum amyloid A amyloidosis (AA) is related to chronic inflammatory disease with prolonged and intense hepatic production of serum amyloid A protein [2]. Amyloid may be found in the interstitium and in the vessels wall of several organs by histology. As recently shown, different etiologies carry distinct prognostic features and therapeutic options, and differential diagnosis and subtyping of amyloid are mandatory [1]. We herein describe a quite unique case of vascular ATTR that was diagnosed in a saphenous vein of an 81-year-old patient undergoing coronary artery bypass graft (CABG) surgery. The diagnosis was allowed by the thorough histological analysis of the remnant saphenous vein that was harvested for CABG.

2. Case report

An 81-year-old man was admitted to our hospital for symptomatic coronary artery disease (CAD) and diagnosed with non-ST-elevation myocardial infarction. Low QRS voltages and T wave changes were also detected on the electrocardiogram. His medical history revealed a silent acute myocardial infarction 10 years earlier, bilateral carotid artery atherosclerosis with ischemic cerebrovascular disease, and arterial hypertension. Coronary angiography showed multivessel CAD with critical stenosis in the left common, the first diagonal, the obtuse marginal, and the right coronary arteries. Shortly after admission, the patient underwent CABG surgery with an autologous left internal mammary artery graft to the anterior descending coronary artery and right saphenous vein grafts to the first diagonal and the obtuse marginal coronary arteries. The intraoperatory echocardiography evidenced moderate (17 mm) increase of the interventricular septum, whereas diastolic dysfunction was not revealed. The remnant segments of the harvested venous and arterial vessels underwent histological analysis immediately after surgery, according to the protocol adopted in our center. Briefly, the vessels were extensively sampled for histology; the specimens were formalin fixed and paraffin embedded; and histochemical (hematoxylin–eosin, Masson's Trichrome, Weigert and Congo Red) stainings were performed on adjacent serial sections. Congo Red staining was

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viewed under polarized light. Based on histological findings, immunohistochemistry was performed on adjacent sections. Briefly, after antigen retrieval and endogenous peroxidase blocking, immunohistochemical stainings were performed by using specific polyclonal antisera raised against transthyretin (1:400 dilution; Dako, Denmark), λ and κ immunoglobulin light chains (prediluted antisera; La Roche Ltd., CA, USA) and Benchmark Ultra Automated Immunostainer (La Roche Ltd.) according to manufacturer's instructions. Reactions were revealed by using 3,3′-diaminobenzidine chromogen substrate, as previously described [4].

The gross features of both saphenous vein and internal mammary artery remnant segments were unremarkable. By light microscopy, the main finding was a moderate and eccentric intimal thickening in the saphenous vein corresponding to amyloid deposits that stained intensely positive for Congo Red (apple green birefringence) and transthyretin (Fig. 1), whereas they showed no immunoreactivity for κ and λ light chains. The left internal mammary artery was free of lesions. Although the surgical procedure was successful, the patient died 1 week later because of diffuse interstitial pneumonia, and no autopsy was performed.

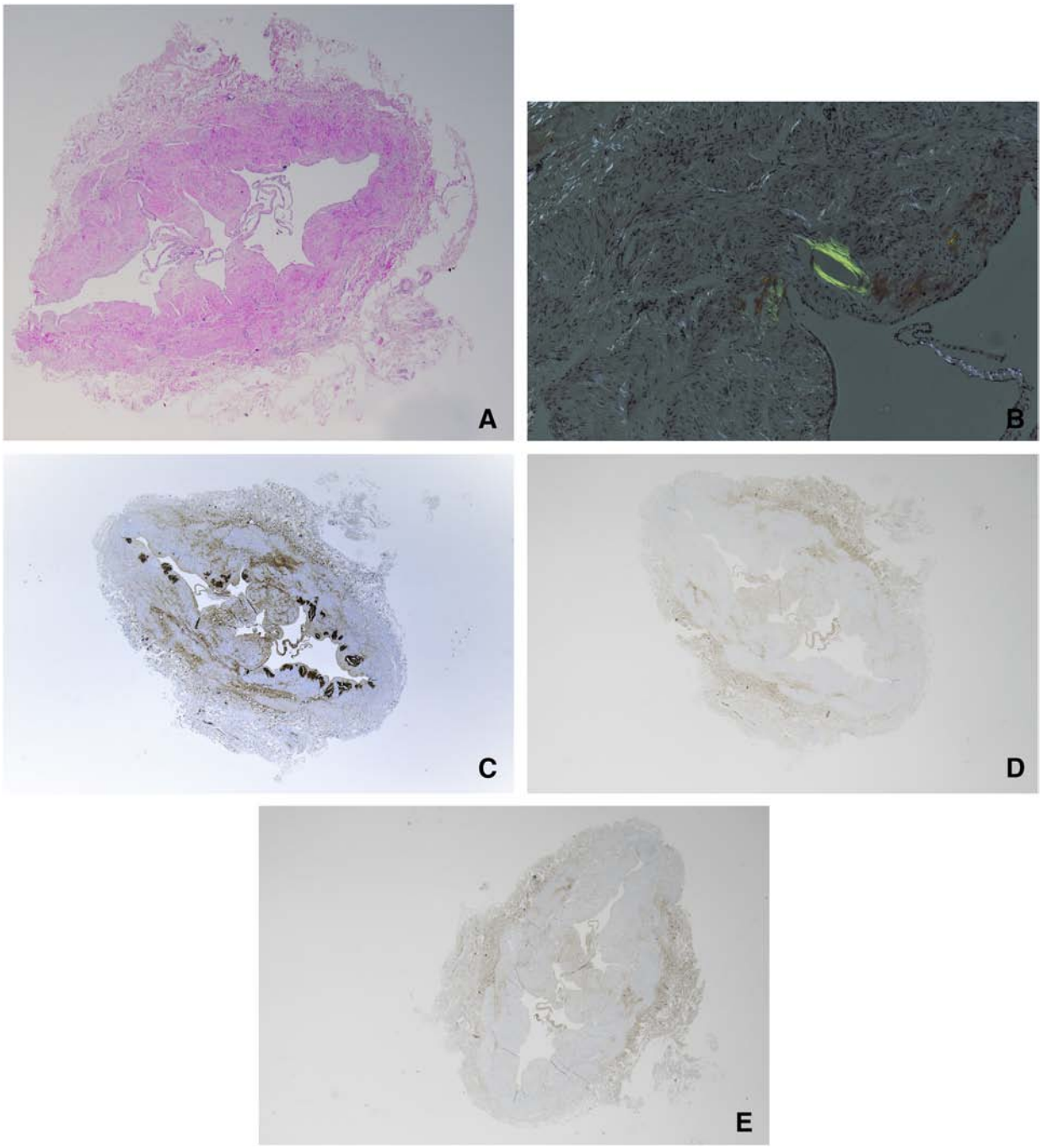

Fig. 1. (A) Eccentric intimal thickening in a saphenous vein harvested from an 81-year-old patient undergoing coronary artery bypass surgery. (B) By Congo Red staining, the intimal thickening was shown to represent amyloid deposits characterized by apple green birefringence under polarized light. (C–E) Amyloid deposits were demonstrated to be strongly immunoreactive for transthyretin (C), whereas they were negative for λ (D) and κ (E) immunoglobulin light chains by immunoperoxidase technique (A: hematoxylin–eosin staining, original magnification 2×; B: Congo Red staining under polarized light, original magnification 10×; C–E: immunoperoxidase technique with hematoxylin counterstaining, original magnification 2×).

3. Discussion

So far, this is the first report demonstrating ATTR in a saphenous vein immediately after CABG procedure. Non-AA and AL were previously diagnosed in two saphenous vein grafts at 10 and 2 years from CABG, respectively, very likely representing an underlying disease [5,6]. Amyloid has also been shown in an arm vein of a patient with venous swelling and monoclonal κ chains in serum and urine [7]. After CABG, saphenous vein grafts may undergo fibrointimal thickening or atherosclerotic changes [8,9], whereas preexisting saphenous vein diseases mainly consist of phlebitic, postphlebitic, aneurysmatic, or thrombotic changes [10]. Vessels (aorta, cerebral and peripheral arteries, so far) may also be involved in storage diseases such as late-onset Pompe disease (a glycogen type II storage autosomal recessive disorder due to mutations in the GAA gene encoding the lysosomal enzyme acid alpha-1,4-glucosidase) [11] and Fabry disease (an X-linked lysosomal storage disease caused by deficiency of the enzyme α-galactosidase A) [12]. In a Fabry patient, a diffuse glycosphingolipid storage was shown in the occluded internal mammary artery graft after 1 year from CABG [13].

Histology is recommended on removed veins and vascular grafts according to a previously proposed protocol [14]. Because of the clinical impact of underdiagnosed infiltrative disorders such as amyloidosis, we do suggest that the remnant saphenous veins and internal mammary arteries harvested for CABG undergo histological analyses that might be implemented by histochemical/immunohistochemical stainings for amyloid, particularly in the elderly population that is more frequently affected by ATTR and nowadays constitutes a significant percentage of patients undergoing cardiac surgery [15].

In the elderly patient of the present report, ATTR of the saphenous vein might likely be due to an unrecognized senile amyloidosis; unfortunately, the patient died shortly after surgery, and no postmortem examination was performed. Indeed, we found low QRS voltages and T wave changes, such as moderate increase of the interventricular septum thickness. These findings are not specific, but they may be consistent with cardiac amyloidosis [2,15]. Because of the urgent CABG procedure and of the postoperative complications (i.e., interstitial pneumonia), the patient had not been further investigated, and no serum protein electrophoresis or serum free light chain analysis was performed. ATTR is the second most common form of cardiac amyloidosis, and its wild-type form is strongly related to aging [1]. In autopsy studies, up to 22%–25% of individuals >80 years old have demonstrable cardiac ATTR, although the degree of deposition is mostly mild [2]. It has also been shown that in elderly (particularly male) patients with aortic valve stenosis, cardiac amyloidosis is not uncommon, especially in cases with low-flow, low-gradient aortic stenosis, and that it carries a worse prognosis [15]. Then, it may be clinically relevant to screen for cardiac amyloidosis in older patients undergoing cardiac surgery or transcatheter aortic valve implantation.

Amyloidosis has a broad range of nonspecific clinical signs and symptoms, including polyneuropathy or autonomic neuropathy, diastolic dysfunction, and conduction defects; because of its clinical heterogenicity, it may be underdiagnosed. Between the different amyloidosis forms, AL amyloidosis is easier to detect by checking monoclonal immunoglobulins and Bence–Jones light chains in serum and urine, whereas ATTR cannot be demonstrated by serum or plasma biomarkers [1]. Then, AL amyloidosis may be more often and/or earlier diagnosed than the other forms. On the other hand, imaging techniques have been proposed for diagnosis of amyloidosis, including echocardiography for cardiac amyloidosis, although so far, the echocardiographic findings are nonspecific [16]. Recently, technetium 99m-pyrophosphate (Tc99m-PYP) myocardial scintigraphy, combined to other diagnostic criteria, has been advocated for noninvasive detection of ATTR [17,18]. As to treatment of ATTR, the recent ATTR-ACT trial showed the effectiveness of tafamidis (i.e., a drug targeted specifically against TTR) in reducing the combination of all-cause mortality and cardiovascular-related hospitalizations in the affected patients [19].

4. Conclusions

Because of population aging, ATTR is becoming an increasingly diagnosed pathology we must be aware of, also in patients undergoing cardiac surgery. Vascular amyloidosis and nonfamilial senile ATTR can be viewed as a component of aging. The identification of the amyloid protein is required in each patient because of distinctive prognosis and therapeutic options. Histology may be helpful for diagnosis as demonstrated in the present report; in our center, all the remnant vascular segments harvested during CABG undergo histology.

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