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Multiple Myeloma And "Non-AL" Amyloidosis: The Importance of Tissue Typing

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Abstract

The most frequent type of amyloidosis complicating Multiple Myeloma is AL amyloidosis. Here we present two rare cases of concomitant Multiple Myeloma and non-AL amyloidosis, one ATTR and one AA amyloidosis, with the aim of underlining the importance of tissue typing. Amyloid identification must always be performed to reach a correct diagnosis allowing, when necessary, a correct therapy.

Keywords: Amyloidosis; Myeloma; TTR

Introduction

Amyloidosis is a heterogenous group of diseases characterized by organised deposition of a misfolded protein in target organs. The identity of the precursor protein distinguishes various types of amyloidosis. About 15% of patients affected by Multiple Myeloma (MM) receive a concomitant diagnosis of immunoglobulin light chain Amyloidosis (AL) where the amyloidogenic protein is a misfolded immunoglobulin Free Light Chain (FLC) produced by clonal plasma cells **[1].** Here we describe two cases of patients affected by MM and concomitant non-AL amyloidosis. Although this association israre, these case reports highlights the importance of tissue typing in every case of amyloidosis even when the AL-type is highly suspicious, because ofan underlyingplasma cell disorder.

Case Series

Case Report 1

A 70-year-old man was admitted to hospital due to heart failure. Fifteen years before, he had coronary angiogram with a chronic occlusion of the right coronary artery and severe stenosis of the left anterior descending, treated coronary angioplasty. Recently, he had a diagnosis of heart failure due to hypertrophic cardiomyopathy and paroxysmal atrial fibrillation. His also had moderate chronic renal failure and hypothyroidism. He had an echocardiogram at our Cardiology Department, characterized by increased biventricular wall thickness (with brilliant, speckled appearance), biventricular systolic dysfunction (left and right 3D ventricular ejection fractions were 35% and 15%, respectively), severe Left Ventricular (LV) diastolic dysfunction, thickened valve leaflets, biatrial dilatation, mild diffuse pericardial effusion and inferior vena cava dilatation with reduced inspiratory collapse. These findings together low electrocardiographic voltages and echocardiographic markedly reduced LV Global Longitudinal Strain (GLS -4%) characterize of relative apical sparing **(Figure 1)** were strongly suggestive of infiltrative cardiomyopathy. 99mTc-DPD scintigraphy showed Peruginiscore III **(Figure 1)**. An internal defibrillator was implanted in primary prevention.

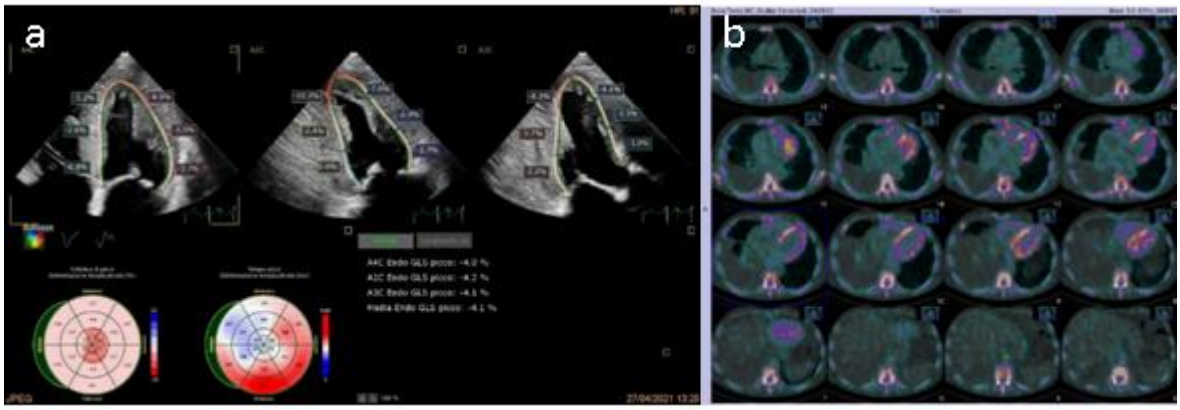

Figure 1: a: Markedly reduced left ventricle GLS with pattern of relative sparing of the apical portions (as represented by bull's eye image in the lower left). b. 99mTc-DPD scintigraphy shows extensive cardiac uptake of bone radiotracer (Perugini score: III).

In the meanwhile, blood exams revealed macrocytic anaemia and markedly increased values of serum Free Light Chain (sFLC) (sFLC kappa 3590 mg/L, sFLC lambda 11.3 mg/L, sFLC ratio 317.69, (dFLC 3578 mg/L)), IgGk M-protein 4.16 g/dL, IgG 6710 mg/dL, and positive Bence Jones. Bone marrow showed diffuse infiltrate (90%) of mature and immature plasma cell elements CD138+ MUM1+ IgG+ with monotypic kappa restriction. Periumbilical fat biopsy and rectal mucosa: negative for amyloid deposits (both Rosso Congo examination and immunohistochemistry). Skeletal Computer Tomography (CT) showed diffuse small vertebral osteolytic lesions.

We concluded for IgGk MM, ISS 3, symptomatic for anemia, renal failure and bone lesions. The patient underwent therapy with daratumumab-bortezomib-melphalan-prednisone rapidly reaching a very good

partial response. Creatinine and hemoglobin returned to normal values while NT-proBNP and troponin were persistently high (539 pg/mL. and 218 ug/L respectively). Afterwards we performed a myocardial biopsy which showed conspicuous interstitial deposits of fibrillar material referable to amyloid, immunoelettroscopy positive for TTR, negative for light chains. The biopsy allowed to diagnose transthyretin cardiac amyloidosis and the patient, while continuing MM therapy, is under evaluation to start therapy with tafamidis.

Case Report 2

A 75-year-old woman presented to our Cardiology Department because of dyspnea and palpitations. She also complained about asthenia, dysphagia and weight loss. An electrocardiogram showed a complete atrioventricular block. Transthoracic echocardiogram showed diffuse thickening of LV wall, normal left and right ventricle ejection fraction (62%, 41% on 3D imaging respectively), biatrial dilatation, mild diffuse pericardial effusion and reduced (-13%) LV GLS with apical sparing. A transesophageal echocardiogram was performed, showing the presence of both left and right appendage thrombosis **(Figure 2 left)**, as previously described in patients with cardiac amyloidosis **[2]**. Furthermore, dense spontaneous echocontrast was visible in both atria, indicative of blood stasis from atrial palsy despite the presence of sinus rhythm. Anticoagulation was started, and a ventricular pacemaker was placed. Complete hematologic evaluation was started:

Blood exams showed IgG 3347 mg/dL, sFLC kappa 1399.2 mg/L, sFLC lambda 3.4 mg/L, sFLC ratio 411.53, (dFLC 1395 mg/L), BNP 2957 pg/mL, TnI 220.8 ng/L, proteinuria 1.63 g/24 hours, Bence Jones positive (30%). Bone marrow examination resulted indiffuse infiltrate (80%) of mature and immature plasma cell elements CD138+ MUM1+ IgG+ with monotypic kappa restriction. Amyloid deposits demonstrated at Congo Red staining and with immunohistochemical staining with anti AA antibodies; anti-kappa and anti-lambda antibodies resulted negative. Rectal mucosa biopsy: amyloid deposits at histochemical and immunohistochemical analyses with antibodies to type AA amyloid **(Figure 2 right)**.

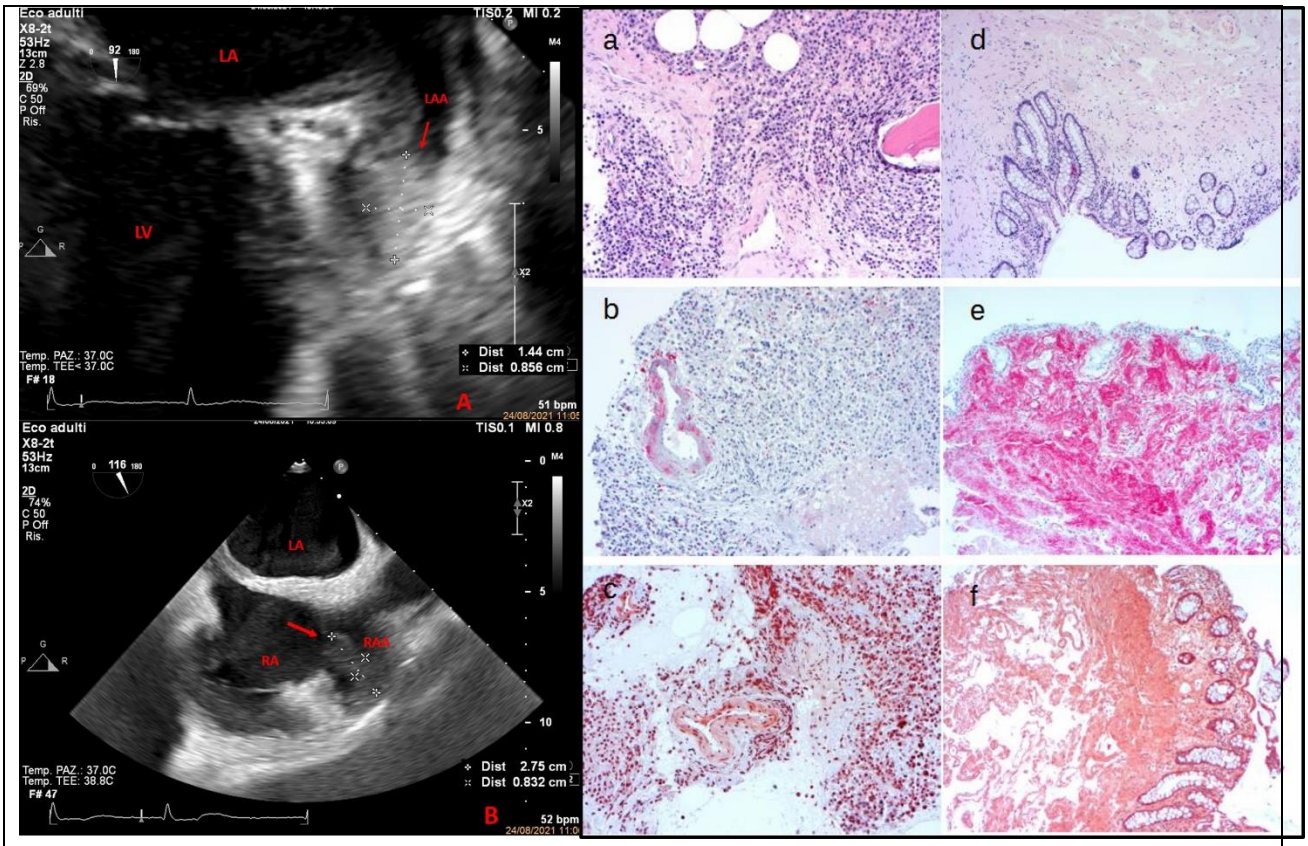

Figure 2: Left: Transesophageal imaging (panel A) and right atrial appendages (panel B). Red arrow indicates in panel A the left atrial appendage thrombus (size: 1.44 x 0.86 mm) and in panel B the right atrial appendage thrombus (size: 2.75x0.83 mm). LA: left atrium LAA: left atrial appendage LV: left ventricle RA: right atrium RAA right atrial appendage**. Right**: a: Bone marrow, hematoxylin and eosin staining 20x; b: Bone marrow, immunohystochemical staining with anti AA antibodies, 10x; c: Bone marrow, Congo Red histochemical staining, 20x; d: Rectal mucosa, hematoxylin and eosin staining, 10x; e: Rectal mucosa, immunohystochemical staining with anti AA antibodies, 10x; f: Rectal mucosa, Congo Red histochemical staining, 10x.

We concluded for IgG kappa Multiple Myeloma ISS 3, symptomatic for hypercalcemia and related AA amyloidosis conditioning infiltrative cardiomiopathy. No other possible underling inflammatory causes were identified. Therapy with bortezomib-melphalan-dexamethasone was started but unfortunately the patient died during the first cycle due to stroke.

Discussion

ATTR amyloidosis is a systemic, life-threatening disease characterized by TTR fibril deposition. A definitive diagnosis of ATTR amyloidosis is often a challenge because of its heterogeneous presentation. Although previously considered untreatable, disease-modifying therapies have recently become available [3]. Its prevalence is unknown but surely higher than previously recognized. Autopsy data from a Finnish study demonstrated that 25% of adults aged> 85 years had myocardial TTR amyloid deposits [4]. When suspected, evaluations include echo and/or CMR imaging to identify any thickening of the cardiac walls. Bone scintigraphy should be performed

if serum/urine immunofixation and sFLC levels are normal; although histological documentation of amyloid remains the gold standard for diagnosis, a bone scintigraphy documenting intense myocardial tracer uptake in the absence of any monoclonal protein can be used to make a definitive diagnosis. Instead, in the presence of a monoclonal immunoglobulin or light chain, a biopsy is required to confirm the presence of amyloid which then should be typed by mass spectroscopy or immunostaining. Identification of a monoclonal protein is not diagnostic of AL amyloidosis as is well documented in our first case: accurate amyloid typing led to diagnosis of TTR amyloidosis in a patient with a concomitant diagnosis of with MM which is rarely described in literature **[5].**

Systemic AA amyloidosis, previously known as secondary/reactive amyloidosis, is a severe complication of some chronic inflammatory diseases where organ damage is the result of extracellular deposition of the soluble acute-phase reactant serum amyloid A protein as insoluble fibrils **[6].** A list of diseases related to AA amyloidosis have been recently updated **[7]** guiding in the evaluation of patients who lack an obvious inflammatory underlying disorder. Identifying the causative disorder allows a target therapy and improves the prognosis. In this recent review, MM and MGUS are listed as unlikely associated to AA amyloidosis. Here we reported the rare case of concomitant diagnosis of MM and AA amyloidosis. While several neoplasias have been associated to AA amyloidosis, its finding by pathological examination ina patient with MM or other monoclonal gammopathy is an unusual situation that requires careful evaluation. These diseases are usually complicated by AL amyloidosis which results from the deposition of light chains produced by the neoplastic clone **[8]** and the association with AA amyloidosis in literature appear to be anecdotal. In a retrospective study Terrè et al reviewed all patients reported in French national amyloid centers presenting with AA amyloidosis and monoclonal gammopathy and performed a literature review from 1946 to 2020. They identified only 12 cases of AA amyloidosis related to monoclonal gammopathy: in all these cases, the monoclonal gammopathy resulted to be the most likely causative event (8 Waldenström macroglobulinaemia, 2 Schnitzler syndrome, 1 MM and 1 MGUS). Thus, AA amyloidosis might rarely complicate lymphoplasmacytic proliferation rather than plasma cell dyscrasia, as illustrated by the presence of the IgM kappa isotype in 84% of the 12 patients. Diagnosis was based on pathological examination showing positive Congo red-stained deposits with green-yellow birefringence and immunohistochemical staining with anti-SAA antibodies, without significant staining by anti-kappa, anti-lambda and anti-transthyretin antibodies. Cases were excluded if another cause of AA amyloidosis was identified. Two treatment strategies can be identified in these cases: the first one is to target clonal proliferation, while the second one is to target the production of acute-phase reactants and SAA by inhibiting their production. The choice is mainly driven by the stage of the underlying neoplasia **[9].** Our case adds to this recent review and to our knowledge represents the third case in literature of proven AA amyloidosis complicating multiple myeloma/MGUS which therefore may represent a rare and poorly known cause of AA amyloidosis. In these cases, the hematologic disorder probably leads to an overproduction of inflammatory cytokines

which is responsible of the low-grade inflammation then causing amyloid deposition.

In conclusion these two case reports highlight the importance of precise identification of amyloid deposits in the case of monoclonal gammopathy/plasma cell dyscrasia as those deposits might not always be light-chain deposition. Incomplete work-up can lead to misdiagnosis sometimes with erroneous therapeutic consequences **(Figure 3)**.

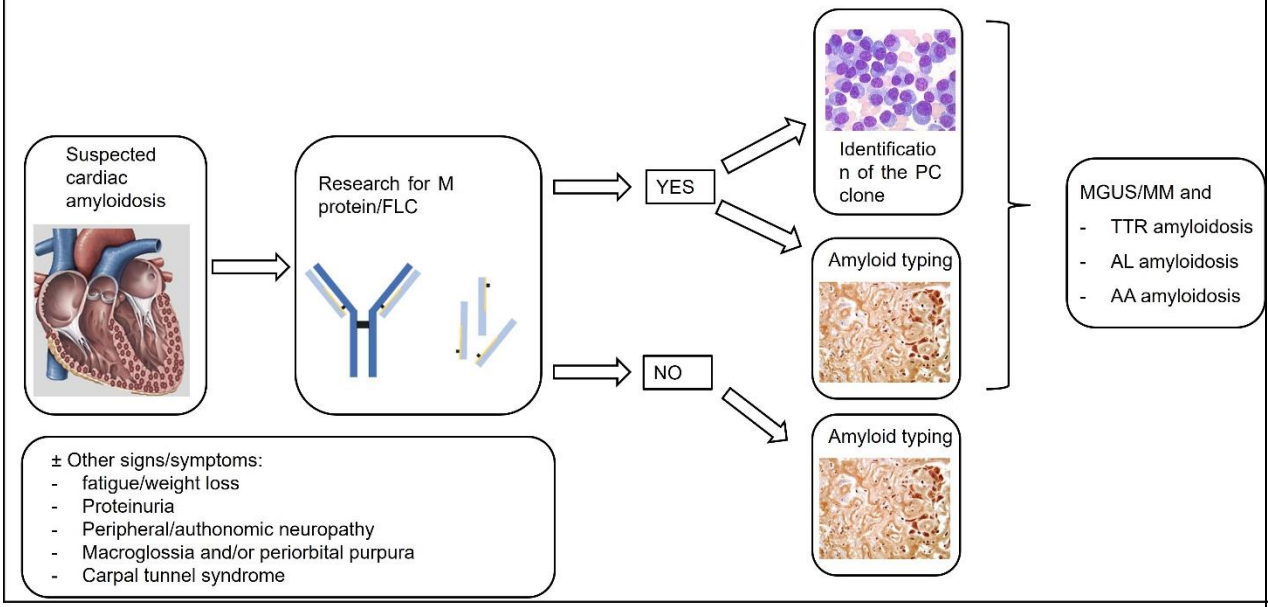

Figure 3: Diagnostic workup of suspected amyloidosis. Amyloid deposits need to be unequivocally typed by reliable techniques (e.g., immunohistochemistry/immunoelctromicroscopy). In the presence of MGUS or abnormal FLC ratio diagnostic workup should proceed with both identification of PC clone and amyloid typing through biopsy (abdominal fat, bone marrow, salivary glands, rectal mucosa or involved organ).

Clinical Practice Points

- Amyloidosis is a heterogenous group of diseases with a heterogenous presentation
- Amyloid identification must always be performed to reach a correct diagnosis
- A correct diagnosis of amyloidosis is important for acorrect therapy

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