Primary Amyloidosis Presenting as Restrictive Cardiomyopathy

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Case Description

A 43-year-old male complained of progressive breathlessness on exertion and dry cough for 6–7 months. At presentation, he was breathless on walking around 10 meters. Along with the breathlessness, he also complained of palpitations on exertion. He also had brief episodes of palpitations at rest for few seconds to a maximum of 1–3 minutes. He complained of upper abdominal fullness and pedal edema for 1 month and exertional chest pain for 20 days. There was no history of giddiness and syncope.

There was no history of diabetes or hypertension. He gave history of (h/o) jaundice 5 years back. He was a nonsmoker and did not consume alcohol. He was second among four siblings. There was no family history of (h/o) heart disease or sudden death.

On Examination

Height 175 cm, weight 78 kg. He had periorbital blackish papules and pedal edema (Fig. 1A). There were no pallor, icterus, cyanosis, or clubbing. Blood pressure in the right upper limb was 96/70 mm Hg supine and dropped to 80/60 mm Hg on standing. Jugular vein pressure (JVP) was raised above the angle of jaw.

Cardiovascular system (CVS): the apex was not palpable; there was no parasternal heave. First and second heart sounds were normal. He had LVS3 and RVS3 were positive; no murmurs were heard. He also had brief episodes of palpitations at rest for few seconds to a maximum of 1–3 minutes. He complained of upper abdominal fullness and pedal edema for 1 month and exertional chest pain for 20 days. There was no history of giddiness and syncope.

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Chest: reduced breath sounds on the right base. There were no adventitial sounds.

Abdomen: liver was palpable 4 cm below the right costal margin. It was soft and mildly tender. The spleen was not palpable and there was no free fluid.

Investigations

ESR: 39 mm in 1st hour.
 Urine Bence Jones proteins: negative.
 Pleural fluid: pleural tap yielded 1.5 L of straw-colored fluid; protein: 5 g%; sugar: 108 mg%; cells: 180; DLC: P60, L40; ADA: 34 U/L.
 ECG: atrial fibrillation with ventricular rate of 68/minute. Low-voltage complexes in limb leads, partial right bundle branch (RBBB), and nonspecific ST-T wave changes.
 X-ray of chest shows gross pleural effusion on right side with massive cardiomegaly. Rest of lung fields are normal along with normal soft tissue and bony cage (Fig. 1B).

Echocardiogram: moderate LVH with maximal left ventricular (LV) wall thickness of 17 mm. Mildly impaired LV contractility, restrictive physiology, mild MR, severe TR, RVSP = 22 + RAP. Inferior vena cava (IVC) dilated, not collapsing with inspiration. Both atriums are markedly enlarged, ventricular cavity is normal in size (Fig. 2).

Abdominal fat pad fine needle aspiration (FNAC) findings: positive for amyloid (received after death) (Figs 3A and B).

Serum electrophoresis: Prominent M band in the γ region in background of marked hypogammaglobulinemia. M protein: quantitatively is 3.8 g/dL. On immunofixation, the M band is of IgG and lambda type (Figs 3C to E).

Urine proteins electrophoresis: negative for proteins (received after death) (Table 1).

Conflict of interest: None


Source of support: Nil

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Course in Hospital

He was diagnosed to have restrictive cardiomyopathy (RCM) likely due to amyloidosis and was managed with IV torsemide, spironolactone, and pantoprazole. Right pleural fluid (1.5 L) was drained that partially relieved breathlessness. Endomyocardial biopsy was planned after correction of coagulogram on July 17, 2016, corrected after giving FFP. The same morning he collapsed in
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the ward, shifted to CCU, and was found to have asystole. He could not be resuscitated and declared dead at 8:02 AM.

Clinical Diagnosis
Restrictive cardiomyopathy likely due to amyloidosis.

Cause of Death
Ventricular arrhythmia, RCM, atrial fibrillation.

Clinical Analysis
He had increased LV wall thickness, mildly impaired LV contractibility, and had typical eye sign of periorbital purpura leading to an undisputed diagnosis of RCM that was associated with amyloidosis because of FNAC of abdominal fat pad showing positive congophilia and serum electrophoresis being positive.

The differential diagnosis includes constrictive pericarditis but there is increased LV wall thickness that is normal in pericarditis and absence of ventricular interdependence, so not considered. Hypertensive heart disease is also unlikely as there is no history of hypertension, no aortic stenosis on echo, and hypertrophic cardiomyopathy is unlikely because of impaired LV contractibility.
Coming to the cause of RCM, in India three common causes include idiopathic/familial RCM, amyloidosis, and endomyocardial fibrosis (EMF) that is not considered based on echo findings.

Idiopathic/familial RCM is ruled out because of no family h/o heart failure (HF)/sudden cardiac death, a slower disease progression of years instead of months, and ECG changes of high/normal QRS voltage while the patient had low voltage.

Out of rare causes of RCM (table) of Fabry disease—cardiac variant points for inclusion is presence of LVH, male predominance, and angina pectoris as prominent features that he had; however, there was no hypertension. Renal involvement may occur but features like lymphedema, neurological pains, neuropathy, and deafness are not seen. Typical findings of angiororders and a slower progression of disease over decades were also not noted. Not to consider Fabry disease

Causes of RCM (less common):
- Hypereosinophilic syndrome
- Radiation
- Doxorubicin
- Scleroderma
- Fabry disease
- Gaucher’s disease
- Hurler disease
- Metastatic cancer
- Sarcoidosis
- Hemochromatosis
- Carcinoid
- Pseudoxanthoma elasticum

So the RCM is because of amyloidosis in this patient and coming to the causes:
- Primary [amyloid light chain (AL)]
- Familial (mutant TTR gene) no family history, age fits (20–70 years) but there is prominent neuropathy in young with sinus node dysfunction and mild cardiac infiltration. Amyloid cardiomyopathy occurs late in the sixth and seventh decades and survival is longer (7–10 years).
- Secondary (SAA)—there was absence of underlying inflammatory condition. Clinical cardiac involvement is uncommon and it predominantly affects kidneys and liver; heart involvement is rare. There is longer survival of >10 years and rapid progression is less likely.
- Senile systemic (wild-type TTR) was not considered because of age (>70 years) and longer survival of 5–7 years.
- Isolated atrial (ANP) was not considered because of involvement of ventricles.

So the RCM is due to AL or light chain-associated amyloidosis, which shows 50% cardiac involvement on initial evaluation out of which 75% have clinical symptoms. The usual age of onset is 50 years with median age at diagnosis being 64 years and only <5% of patients are under the age of 40 years. They present as rapidly progressive HF; the HF is biventricular but right-sided features predominate as seen here. The postural hypotension as seen here and exertional syncope due to low cardiac output is noted. The periorbital purpura (raccoon eye sign) is virtually pathognomonic of AL amyloidosis. MacroGLOSSIA is usually seen but was not identified in this case. Other clinical features like low volume pulse, postural drop of BP, raised JVP, AF, LV53, RV53+. Pleural effusion and hepatomegaly are due to HF. Proteinuria was mild and not in nephrotic range. Low-voltage complexes on ECG were seen. Q waves in V1–V3 were not seen and echo findings suggestive of amyloidosis were noted as thickened LV and RV walls with normal-sized ventricular cavities and bialtrial enlargement.
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Based on the International Myeloma Working Group diagnostic criteria 2014, three of the criteria were met in this patient such as:

• Presence of an amyloid-related systemic syndrome—heart.
• Positive amyloid staining by Congo red in any tissue—fat pad aspirate.
• Evidence of a monoclonal plasma cell proliferative disorder—presence of a serum M protein.

Evidence that the amyloid is light chain-related disease is not there.

The other organs involved: macroglossia—nil, kidneys—no proteinurin/protein+ maybe, liver—congestive hepatomegaly, spleen—not palpable, arthropathy—no, cardiac tunnel syndrome—no, peripheral nervous system—postural drop of BP and GI symptoms—maybe.

Was multiple myeloma associated with AL amyloid? About 10% of AL amyloidosis patients have multiple myeloma, whichshow
>30% plasma cells in the bone marrow. However, bone marrow biopsy was not done. There was no h/o bone pains, absence of hypercalcemia, and lytic lesions.

Can Waldenström macroglobulinemia be associated with AL amyloidosis? It is but very rare. Cardiac involvement is uncommon. High incidence of lymph node and soft tissue involvement is seen, which was not noted in this patient.

Was it IgD associated with AL amyloidosis? Rare (53 of 3,995 patients—1.3%). Renal and cardiac involvement less common.1

The cause of death was sudden cardiac death due to ventricular tachyarrhythmias. Conduction block was less likely since baseline QRS was narrow; there may be partial block.

Final Clinical Diagnosis

• Primary amyloidosis (D/D multiple myeloma)
• Restrictive cardiomyopathy
• Heart failure
• Atrial fibrillation
• Cause of death: likely ventricular tachyarrhythmia

Clinical Discussion

Prof KL Gupta: So there was diagnosis of AL amyloidosis with RCM. Not sufficient evidence for multiple myeloma (MM). Pleural effusion that is exudative is difficult to base on cardiac failure.

Prof Rajesh Vijay Vergia: It is a clear case of AL type of amyloidosis on echo cardiograph findings. There is in addition marked atrial septal thickening due to amyloidosis and possibly kidney involvement.

Dr Inderpal: Pleural effusion being exudative can be due to involvement by amyloidosis of pleura.

Prof Pankaj Malhotra: What is the possible cause of coagulopathy?

Urine was tested by the qualitative method, which showed albumin nil probably tested by the dip stick test.

Should have gone for quantitative protein urine estimation.

Prof Manphool: Comment on emerging role of cardiac MR in subclinical cases of MM when associated with cardiac involvement. Cardiac MR is a gold standard tool and can replace endocardial biopsy. The findings are very typically seen as Zebra type of enhancement.

Prof Sanjay: I would like to add two more organs involved by primary amyloidosis. One is adrenal gland because of persistent hyponatremia. Second, hypoalbuminemia could be because of kidney involvement. Even the cardiac involvement by amyloidosis is seen as involvement of atrium, ventricles, conduction system, and valves. Coronaries are involved. The coagulopathy can be explained by liver per say or presence of an inhibitor.

Prof Manish Rathi: For urine electrophoresis where you need to do light-chain analysis you require 24-hour urine sample and a random urine sample will not yield protein.

Prof Neelam Varma: Amyloidosis is unlikely MM as no CRAB; the coagulopathy is explained by factor 10 attaching to amyloid protein.

Prof Pankaj Malhotra: The hyponatremia is pseudo-hyponatremia as potassium is normal. In plasma cell dyscrasias, sodium is falsely low because of displacement of water by high globin content of blood.

Prof Ajay Behl: AR cannot be considered here as it is a systolic dysfunction while this patient had a diastolic dysfunction. The coagulogram derangement can be due to amyloidosis but in patients of HF due to congestion the coagulogram can be abnormal and patients of HF before doing a biopsy often need correction.

Prof KL Gupta: All agree to the diagnosis of primary amyloidosis, and everybody has discussed the various aspects of the disease.

Pathological Findings

A partial autopsy was done.

Serosal Cavities

400 mL pale-colored fluid in both plural cavities and 150 mL in pericardial cavity. Peritoneal cavity—3 L pale-colored fluid. There was a blood clot in the right lung base.

Heart

Heart was massively enlarged and weighed 540 g. Gross: it was firm, stiff, and pale brown in color on the pericardial surface. Thrombus was seen in both the auricles and were hypertrophied. The endocardium of both R and L atrium was opaque and thickened with flattening of musculature. The tricuspid valve and the mitral valve were thickened. Both ventricular cavities were narrowed with endocardium being relatively normal. There was LV and RV hypertrophy measuring 1.8 and 0.8 cm, respectively (Fig. 4). The pulmonary valve and pulmonary artery showed some granularity. Coronaries within normal limits do not showed atherosclerotic changes. Micro: there was deposition of the pale eosinophilic amorphous material in the subendocardial region, interstitium, surrounding the myocytes (pericellular). It is present in the myocardium replacing myocytes along with valvular involvement. Prominent change was that all vessels show similar material deposition in their wall with luminal narrowing causing ischemic changes of the myocardium; however, the major coronary arteries were normal with only the adventitia showing similar deposits (Figs 5A to D). This material is congophilic with apple green birefringence under polarized light (Fig. 5E). Focally amyloid deposition of amyloid present-type of amyloidoma. Electron microscopy: fine crisscross fibrils of amyloid confirmed both perivascular and interstitial. IHC: SAA—weak positive, kappa—negative, lambda—inconclusive (Fig. 6).

Bone Marrow

Increased number of plasma cells with nodular collection having binucleate and multinucleate forms. IHC: kappa—negative, lambda—positive, CD138—strongly positive, and CD 38—weakly positive. Hemopoietic elements depressed (Fig. 7).

Lymph Nodes (Hilar and Mesenteric)

Nodal architecture replaced by sheets of plasma cells with binucleation. IHC: positive for CD 138, weak CD 38 and lambda,
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Lungs (wt. 840 g) G/A
Subcrepitant. Microvascular and interstitial deposition of amyloid. Prominent interstitial vessels with medial hypertrophy and intimal proliferation (Fig. 8A).

Spleen (wt. 160 g)
Depletion of white pulp, red pulp congestion. Amyloid deposition in splenic arterioles. No deposition in the interstitium (Fig. 8B).

Liver (wt. 1,400 g) G/A
Firm in consistency with alternate pale and dark areas and vague nodularity. Microvascular deposition of amyloid within portal tracts,

kappa—negative. There was capsular and capsular deposition of amyloid and around vessels.

Adrenals
Periadrenal vessels and fat show nodular deposits of amyloid. There was focal infiltration.

Kidneys (wt. 500 g) G/A
Cortical cyst on left side. Micro: deposition of congophilic material around small-sized vessels. The arcuate and segmental arteries essentially normal. Glomeruli and interstitium normal. No cast nephropathy present.
which is patchy. Centrilobular necrosis with sinusoidal dilatation and collapse reticulin.

**Pancreas and GIT**
Vascular deposits of amyloid present (Fig. 8C).
Skeletal muscle showed mild lymphocytic infiltrate with patchy amyloid deposition.
Testes deposition localized to the paratesticular region and interstitium. Atrophy of the seminiferous tubules. Testicular and bladder vessels also show amyloid deposition.

**Final Autopsy Diagnosis**
K/C/O of RCM with
- Amyloid cardiomyopathy (myeloma associated: M band positive, lambda restriction)
- Systemic AL amyloidosis: (predominantly vascular) kidneys, lungs, liver, spleen, adrenals, gastrointestinal tract, pancreas, testes, urinary bladder, lymph nodes, and skeletal muscle

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**Fig. 6:** Fine crisscross fibrils of amyloid on electron microscopy

**Figs 7A to F:** (A) Nodal architecture replaced by sheets of plasma cells; (B) Increased number of plasma cells with nodular collection in marrow; (C) Sheets of plasma cells few showing binucleation; (D to F) Positive for CD 138, weak CD 38, and lambda

**Figs 8A to C:** Vascular deposition of amyloid in lung, spleen, and intestine
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- Pulmonary arteriopathy
- Passive congestion—liver, lungs

**Final Discussion**

Prof Uma: Amyloid cardiomyopathy is a rare. Around 10% of patients with multiple myeloma develop systemic light-chain amyloid disease with a mean age of 64 years. Cardiac screenings are needed in all patients with multiple myeloma. Typical case of multiple myeloma may present with cardiac amyloidosis (RCM). Other proteins to be searched vitronectin a multifunctional glycoprotein synthesis by liver and vascular smooth muscle cells which are toxic and has amyloidogenic propensity.

Prof Ajay Behl: Important to do a bone marrow aspiration and biopsy for the work-up amyloidosis.

Prof Sanjay Jain: Interesting distribution of amyloid being mainly perivascular and in the heart. Important point to be highlighted is that structural changes may not always produce damage but functional changes cause symptoms. As Sir William Osler said 100 years ago, "Longevity is a vascular question of compliance and a person is as old as his arteries are compliant." There is loss of compliance of the vessels because of amyloid deposition and reason why the liver, adrenal, and kidney are deranged along with malabsorption.

Prof Pankaj: Amyloid was deposited in an interstitial pattern in only heart and lung while other organs showed vascular deposit. Did the pleural and peritoneal surfaces show amyloid deposition?

Prof Uma: Interstitial pattern of deposits were in heart only. In the lung, they were focal and mainly vascular. No deposits were seen in the pleura or peritoneum. AL was one type of protein.

Prof Varun: Dr Uma, why the predilection for heart was there and is there a genetic basis for it?

Prof Uma: When we talk of idiopathic cardiomyopathy, we look for genetic basis but in this case the cause of amyloidosis was MM and no genetics was done.

Prof Radotra: Can you explain the SAA IHC being positive in MM?

Prof Uma: SAA was weakly positive but there was lambda restriction.

Prof KL Gupta: Thank you everyone.

**References**