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Diagnostic Approach to Cardiac Amyloidosis

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Amyloidosis is a relatively rare disease that may be underdiagnosed and could affect the entire human body. Many organs may be affected, which could increase the morbidity and mortality. Cardiac involvement is the leading cause of poor prognosis. Patients with cardiac amyloidosis are usually admitted with heart failure. The clinical presentation varies greatly, and using the correct approach is important in identifying cardiac amyloidosis.

A 51-year-old man was diagnosed with chronic heart failure. He had increased brain natriuretic peptide levels, a low ejection fraction, and left and right ventricular hypertrophy with granular sparkling as seen by echocardiography. These findings led us to perform a cardiac biopsy that confirmed the diagnosis of cardiac amyloidosis. Further investigation revealed that the patient had amyloid light-chain type amyloidosis due to multiple myeloma. He is now undergoing the 3rd phase of chemotherapy.

Congo-red stain is usually used by physicians to histologically confirm amyloidosis, with which apple-green birefringence indicates amyloid deposits. Other stains such as direct fast scarlet (DFS) and hematoxylin-eosin (HE) can also confirm the presence of amyloid deposits. In the present case, DFS and HE were used, both of which suggested amyloid deposits surrounding myocardial cells. The use of a combination of stains can increase the diagnostic sensitivity and specificity of amyloidosis. However, the typical echocardiographic appearances would be enough to diagnose cardiac amyloidosis when it is impossible for the patient to undergo a cardiac biopsy, if an additional histological specimen from another tissue such as abdominal fat confirms amyloidosis.

Amyloidosis is an uncommon disease that is probably underdiagnosed. It is a systemic disease caused by the deposition of misfolded protein fibrils, and may occur in any organ. Frequently affected organs are the heart, kidney, liver, and spleen.[1] The involvement of multisystem organs leads to increased morbidity and mortality. Cardiac involvement is a leading cause of morbidity and mortality, especially in specific types of amyloidosis such as primary amyloidosis due to amyloid light-chain (AL) accumulation.[2] Other types of amyloidosis such as secondary amyloidosis, including amyloid A (AA) type, may also affect the heart, although rarely.

The clinical presentation varies greatly, but usually patients with cardiac amyloidosis are admitted with heart failure. This case report focuses on how to approach cardiac amyloidosis, and hopefully, it will contribute to the correct diagnosis and treatment of this disease.

CLINICAL CASE

A 51-year-old man was referred to our hospital. He had suffered from recurrent dyspnea at rest and exertion, paroxysmal nocturnal dyspnea, pretibial edema, and general fatigue for twelve months. On previous admission at another hospital three months before, chronic heart failure with myocardial hypertrophy of unknown etiology was identified. He had received the oral diuretic drugs furosemide (20 mg) and spironolactone (25 mg). However, there was no improvement in the symptoms, and they gradually worsened. He was classified as having New York Heart Association (NYHA) class IV heart failure, and was admitted to our hospital. There were no other symptoms, such as chest pain, body weight loss, or persistent diarrhea.

The patient consumed two bottles of 250 ml beer/day, and did not have a smoking habit. There was no significant family history of heart disease or past history of hypertension, coronary artery disease, or metabolic disease. The physical examination revealed that he was alert, his body mass index was 20.2 kg/m^2, his blood pressure was 100/58 mmHg, his heart rate was 100 bpm, his respiratory rate was 26 breaths/min, and he was

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afebrile. An enlargement of the left heart border, a third heart sound, and anasarca were observed. On lung examination, we found that he had a bilateral coarse crackle at the bases. There seemed to be no abnormal dilatation of the jugular vein, icteric sclera, macroglossia, arthrocele, or capillary fragility resulting in easy bruising. Although hepatosplenomegaly was not identified, ascites retention was suspected from soft and undulating abdominal distension. Blood results showed an increased brain natriuretic peptide (BNP) level of 1381 pg/ml. The level of albumin was 2.4 g/dl, which was decreased. Serum protein electrophoresis did not demonstrate the typical M-peak. Liver enzymes levels slightly increased, and estimated glomerular filtration rate was mildly decreased (Table I). Electrocardiography (ECG) showed normal sinus rhythm with an indeterminate QRS-axis, low voltage in limb leads, P-sinistrocardiale, and precordial poor R progression (Figure 1). Chest radiography demonstrated cardiomegaly with a cardiothoracic ratio of 69.3% and bilateral pulmonary congestion (Figure 1). Echocardiography showed a low ejection fraction (EF) of 42.2% with a restrictive pattern of transmitral flow, which indicated coincident diastolic dysfunction, left and right ventricular hypertrophy with granular sparkling (Figure 2), and mild mitral regurgitation. End-diastolic thickness of the interventricular septum and left ventricular posterior wall were 14 mm and 15 mm, respectively. ^{99m}Tc-pyrophosphate scintigraphy revealed diffuse cardiac accumulation (Figure 3). Coronary angiography findings were normal (Figure 4).

Table I. Laboratory data

Peripheral blood		**Serology**	
White blood cells	6000/μl	Immunoglobulin G	472 mg/dl
Red blood cells	434×10^3/μl	Immunoglobulin A	119 mg/dl
Hemoglobin	13.8 g/dl	Immunoglobulin M	25 mg/dl
Hematocrit	39.3%		
Platelets	34.5×10^3/μl	β2-microglobulin	2.9 mg/l
Biochemistry		M protein (Immunofixation)	(+)
Sodium	135 mEq/l	Free light chain (κ)	(−)
Potassium	4.7 mEq/l	Free light chain (λ)	490 mg/l
Chloride	98 mEq/l		
Calcium	8.0 mg/dl	Complement component 3	110 mg/dl
Phosphate	3.8 mg/dl	Complement component 4	33.6 mg/dl
Urea nitrogen	18 mg/dl	Antinuclear antibody	(−)
Serum creatinine	0.8 mg/dl	Rheumatoid factor	(−)
Estimated glomerular filtration rate	80.6 ml/min/1.73m^2		
Uric acid	5.2 mg/dl	Hepatitis B virus antigen	(−)
Total protein	4.8 g/dl	Hepatitis C virus antibody	(−)
Serum albumin	2.4 g/dl		
Asparate aminotransferase	41 IU/l	White blood cell α-galactosidase A activity	50.1 nmol/mg protein/h
Alanine aminotransferase	52 IU/l		
Alkaline phosphate	179 IU/l	**Urinalysis**	
Lactate dehydrogenase	331 IU/l	Protein (qualitative)	(+)
Total cholesterol	139 mg/dl	Glucose	(−)
Triglycerides	87 mg/dl	Urinary red blood cells	(−)
		Granular casts	(−)
Electrophoresis		Fatty casts	(−)
Albumin	52.4%	Bence-Jones protein (Immunofixation)	(+)
α1-globulin	6.5%	Protein (quantitative)	285 mg/day
α2-globulin	16.6%		
β-globulin	12.1%		
γ-globulin	12.4%		

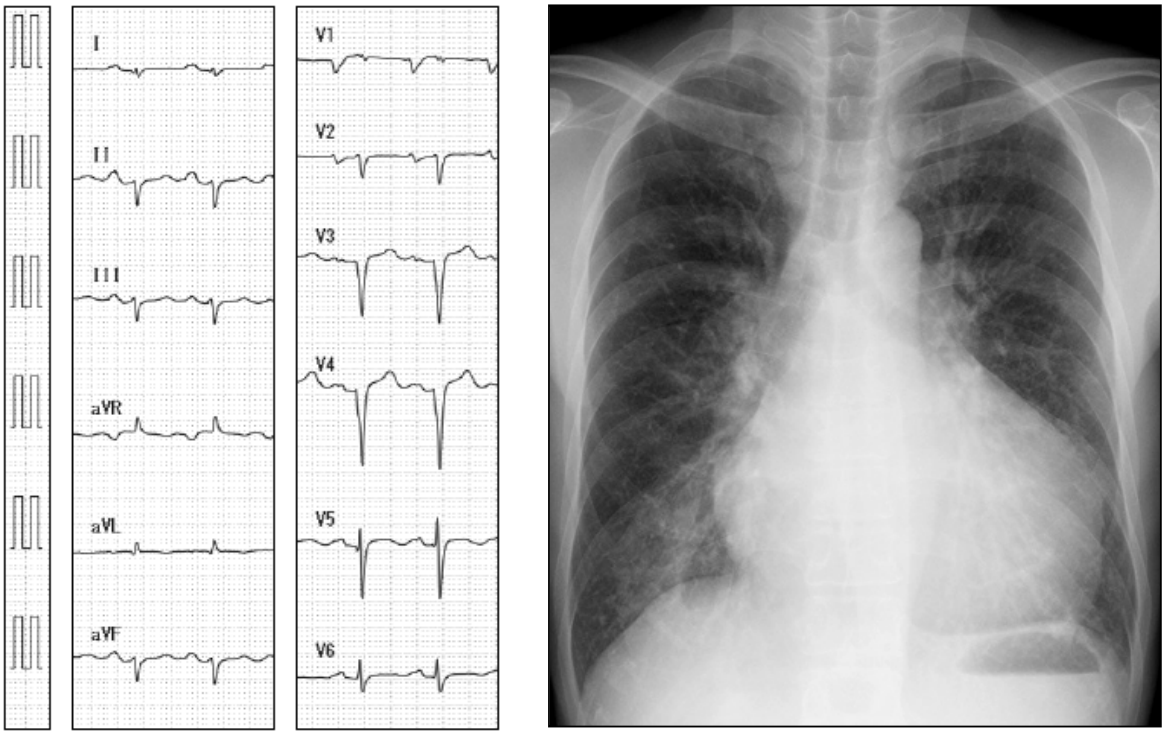

Figure 1. Electrocardiographic and chest radiographic findings.
Electrocardiography (left panel) showing normal sinus rhythm with an indeterminate QRS-axis, low voltage in limb leads, P-sinistrocardiale, and precordial poor R progression. Chest radiography (right panel) demonstrating cardiomegaly with a cardiothoracic ratio of 69.3% and bilateral pulmonary congestion.

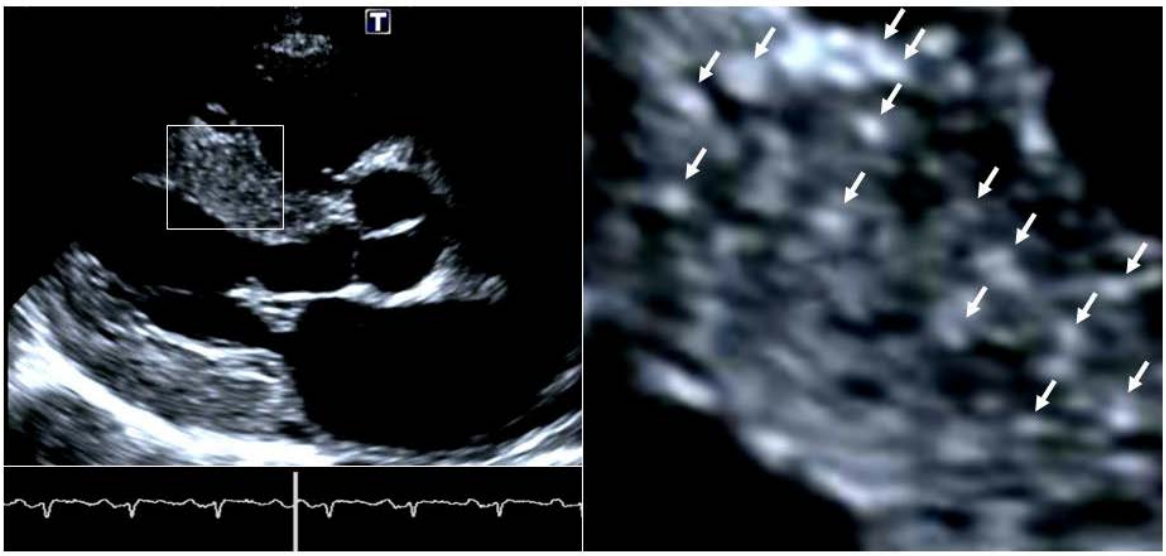

Figure 2. Echocardiographic findings.
The white open box in the left panel is enlarged in the right panel. Left ventricular hypertrophy with granular sparkling (white arrows) is noted.

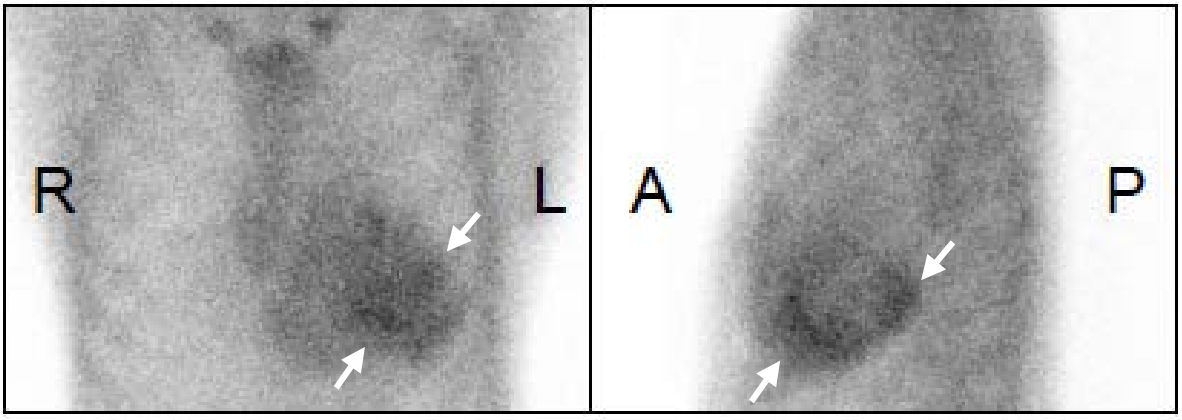

Figure 3. ^{99m}Tc-pyrophosphate scintigraphic findings.
Diffuse cardiac accumulation (white arrows) is noted.

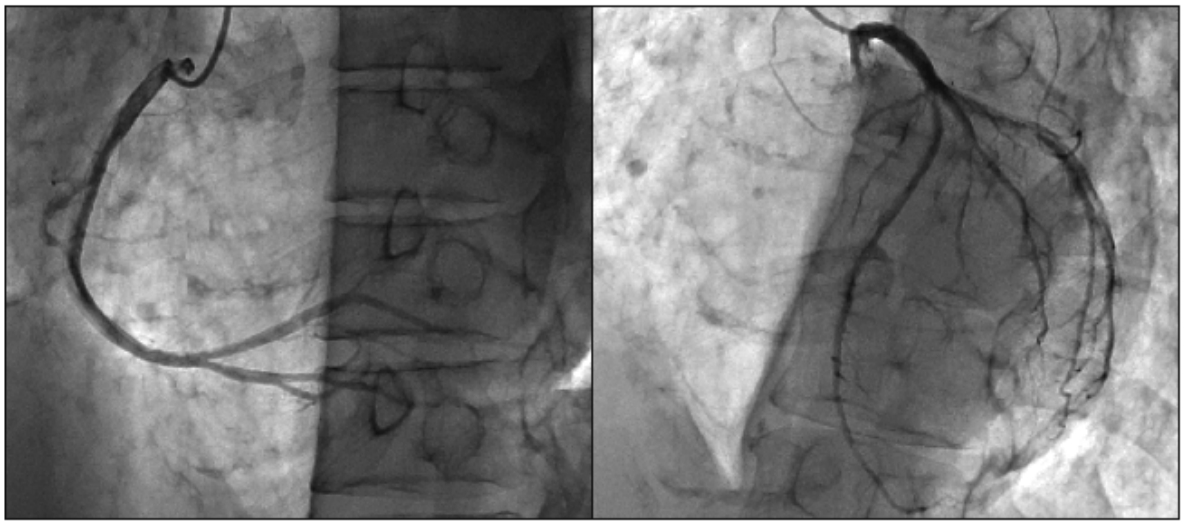

Figure 4. Coronary angiographic findings.
No significant lesions are observed in the right (left panel) or left (right panel) coronary arteries.

These findings led us to suspect cardiac amyloidosis. We then performed a cardiac biopsy that confirmed AL type amyloidosis. The stains that we used were direct fast scarlet (DFS) and hematoxylin-eosin (HE). On DFS staining, we found orange amyloid deposits surrounding darker blue myocardial cells (Figure 5). On HE staining, we found an amorphous light pink material, suggesting amyloid deposits, surrounding darker pink myocardial cells (Figure 5). Immunostaining results were compatible with AL amyloidosis, with positive λ-chain staining, and negative κ-chain and AA staining (Figure 6).

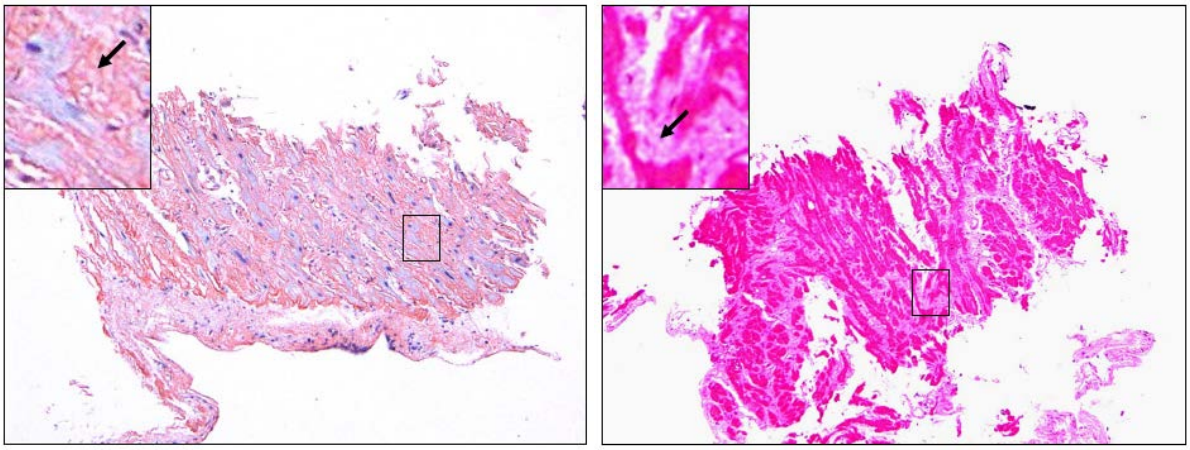

Figure 5. DFS (left panel) and HE (right panel) staining of the right ventricle specimen at 10× magnification.
The black open boxes are enlarged in the upper left corner of each panel. DFS staining (left panel): The orange amyloid deposits (black arrow) surround darker blue myocardial cells. HE staining (right panel): The amorphous light pink amyloid deposits (black arrow) surround darker pink myocardial cells.

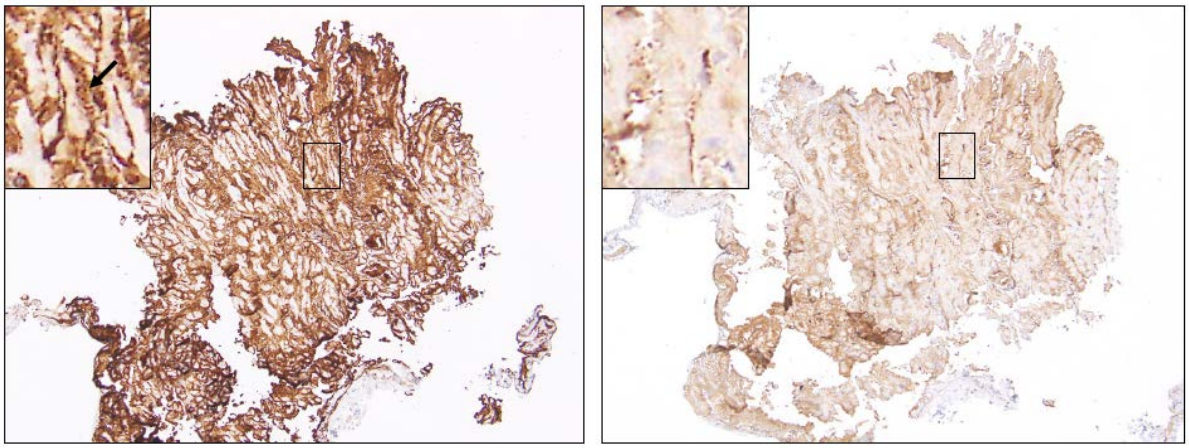

Figure 6. λ-chain (left panel) and κ-chain (right panel) immunostaining of the right ventricle specimen at 10× magnification.
The black open boxes are enlarged in the upper left corner of each panel. The dark brown area indicated by the black arrow in the left panel denotes the λ-chain positive area surrounding unstained myocardial cells. The right panel exhibits negative κ-chain staining.

Urinalysis demonstrated proteinuria of 1+. Moreover, an immunofixation assay revealed the presence of Bence-Jones protein (BJP) in urine and M protein (free light-chain, dominant λ-chain) in serum (Table I). Therefore, the patient was suspected of having multiple myeloma. He underwent bone marrow aspiration (BMA), which showed an abundance of plasma cells (10%). This confirmed the diagnosis of multiple myeloma (BJP-λ type), and we concluded that the patient had cardiac AL amyloidosis due to multiple myeloma.

At the time of this writing, the patient completed the 2nd phase of dexamethasone combined with melphalan for the treatment of multiple myeloma. Treatment for heart failure included losartan (25 mg), carvedilol (1.25 mg), spironolactone (25 mg), furosemide (40 mg), and azosemide (30 mg). The patient is in the cardiology medical ward with stable vital signs and relieved symptoms. However, he is still under close observation, as he has just started the 3rd phase of chemotherapy.

DISCUSSION

The patient had been suffering from recurrent dyspnea at rest and exertion, paroxysmal nocturnal dyspnea, pretibial edema, and general fatigue for the past year. From the previous admission at another hospital, he had been known to have myocardial hypertrophy and chronic heart failure. On the physical examination, vital signs were stable, but he had an enlargement of the left heart border, a third heart sound, bilateral rales at the lung bases, and anasarca. Although the distended jugular vein and hepatosplenomegaly were difficult to detect, they might have been masked by severe anasarca. These data led us to diagnose the patient with chronic NYHA class IV heart failure.

Next, we proceeded to assess the heart failure etiology. On blood examination, we found increased BNP and low albumin levels. High BNP levels generally indicate a high filling pressure. In addition, patients with amyloidosis may have relatively high BNP levels due to augmented gene expression.[3] The increased amount of BNP could also indicate a poor prognosis. P-sinistrocardiale in ECG reflected overloading of the left atrium, and low voltage in limb leads indicated anasarca. Echocardiography revealed a decreased EF with diastolic dysfunction, and left and right ventricular hypertrophy with granular sparkling, which would indicate secondary hypertrophic cardiomyopathy due to cardiac amyloidosis. According to the diagnostic algorithm (Figure 7),[4] other supportive information from cardiac imaging, including ^{99m}Tc-pyrophosphate scintigraphy, also suggested cardiac amyloidosis. From urinalysis, we found BJP, which suggested the existence of multiple myeloma. After that, the patient underwent BMA, which showed an abundance of plasma cells. This confirmed the diagnosis of multiple myeloma. About 10–15% of multiple myeloma patients develop amyloidosis.[5] AL amyloidosis is the commonest form of amyloidosis that associated with a plasma cell dyscrasia.[1] Finally, cardiac AL amyloidosis was confirmed by the cardiac biopsy.

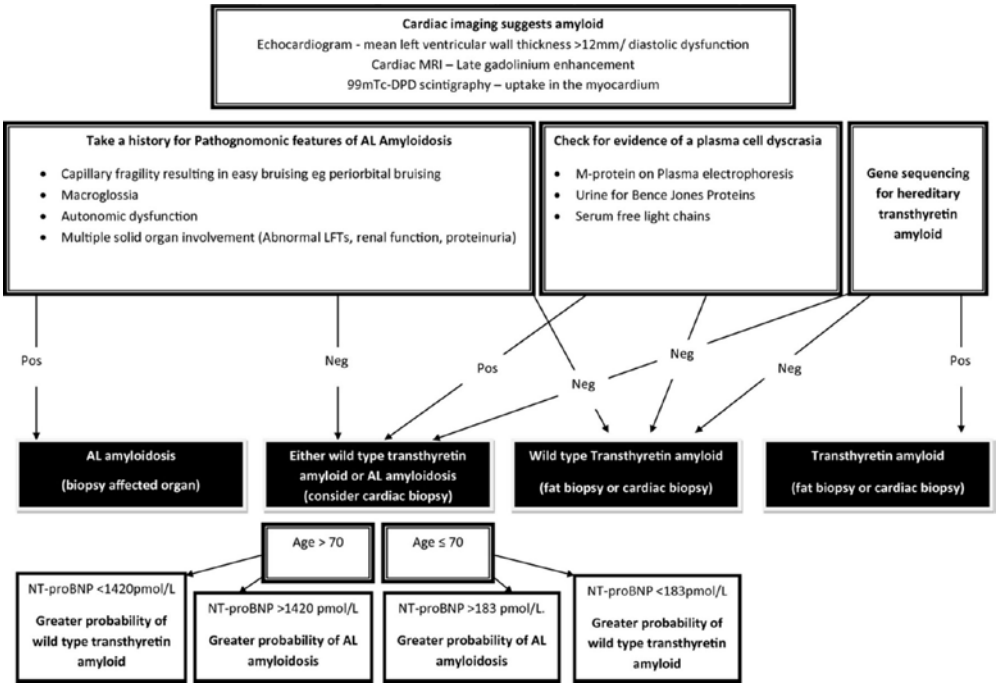

Figure 7. Cardiac amyloidosis diagnostic algorithm.[4]

Banypersad et al, stated that to confirm the diagnosis of cardiac amyloidosis, a cardiac biopsy should be performed.[6] The typical stain used is Congo red, which stains amyloid deposits with a birefringent apple-green color. Other staining methods such as DFS, HE can also confirm the amyloid deposits. As demonstrated in Figure 5, DFS stained amyloid deposits orange, and HE staining resulted in an amorphous light pink material that indicated amyloid deposits surrounding myocardial cells. The combination of stains increases diagnostic sensitivity and specificity. However, Falk stated that if it is impossible for the patient to undergo cardiac biopsy, the typical echocardiographic appearances of the hearts is sufficient for the diagnosis of cardiac amyloidosis, when an additional histological specimen from another tissue such as abdominal fat is used to confirm amyloidosis.[1] In addition, coronary angiography is necessary to rule out coronary artery disease.[7]

Cardiac amyloidosis management consists of two parts, which are to treat the underlying disease and to treat the cardiac-related symptoms.[1] The heart is affected in approximately 60% of patients with AL amyloidosis, with congestive heart failure symptoms presenting in about 70% of these patients.[8] Treatment for multiple myeloma of the patient in this report has reached the 3rd phase of chemotherapy, which consists of dexamethasone combined with melphalan. In a previous study, high-dose melphalan and stem-cell transplantation resulted in a complete hematologic response in 40% of patients.[9] Hopefully, these therapy regimens will improve the general status of the patient. Unfortunately, the advanced nature of cardiac disease in many patients at the time of diagnosis either renders them unfit for high-dose chemotherapy with autologous stem cell replacement or places them at a risk of peritreatment mortality as high as 30%.[1] Dexamethasone could also aggravate heart failure. Therefore, tight observation has to be applied when these regimens are started for patients with cardiac amyloidosis. In treating cardiac-related symptoms, other supportive treatments were used to relieve the symptoms and to protect against progressive cardiac functional deterioration. There was no anticoagulant use, as the value of its routine use for patients with severe heart failure remains uncertain.[1] It would be used if any strong indication such as atrial fibrillation existed. The patient is now still in a cardiology medical ward with stable vital signs and needs to be carefully observed as he has just started the 3rd phase of chemotherapy. Patients with heart involvement have a median survival of only 1.08 years. Further, with the occurrence of congestive heart failure, the median survival duration decreases to 0.75 years.[8]

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