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Review

Recent advances in diagnosis and treatment of cardiac amyloidosis

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ABSTRACT

Cardiac amyloidosis (CA) has been believed to be a rare disease for a long time, but recent sophisticated diagnostic modalities demonstrate that a considerable number of CA patients are hidden among those diagnosed with heart failure. Prognosis of CA was poor, but recent developments in therapeutic interventions have improved survival in these patients. Therefore, early detection and precise diagnosis is clinically important. In this review article, we overview recent progress in diagnosis and treatment for CA.

Contents

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Introduction

The number of patients with heart failure (HF) is increasing especially in an aging society such as Japan, and the situation is currently called "Pandemic of HF" [1]. It is apparent that half of the HF patients have HF with preserved ejection fraction (HFpEF). Much attention has been paid to HFpEF, because mortality of HFpEF is comparable to that of HF with reduced ejection fraction (HFrEF) [2]. In contrast to HFrEF, there are no evidence-based medical treatments to improve the prognosis of HFpEF.

Amyloidosis is defined as organ dysfunction due to deposition of β-sheet structured amyloid fibril in multiple organs. Amyloidosis is divided into local and systemic amyloidosis, and systemic amyloidosis is further divided into several subtypes depending on the context of amyloid fibrils (Table 1). Cardiac involvement is the most significant predictor for poor prognosis in patients with systemic amyloidosis. Cardiac amyloidosis (CA) is a progressive infiltrative cardiomyopathy characterized by restrictive cardiomyopathy and presentation with conduction system diseases. CA has been believed as a rare disease for a long time, but recent sophisticated diagnostic modalities revealed that considerable number of CA patients are hidden in HF, especially in HFpEF [3].

Prognosis of CA was poor, but recent progress in therapeutic interventions has contributed to improvement of prognosis in these patients. Treatment strategies of CA vary greatly depending on the context of amyloid fibril precursor such as chemotherapy, liver transplantation, and novel transthyretin (TTR)-modifying therapeutics, therefore, early detection and precise diagnosis is necessary for optimal treatment. In this review article, we summarize recent progress in diagnosis and treatment for CA.

Cardiac amyloidosis that cardiologists often encounter

As shown in Table 1, several amyloidogenic proteins cause systemic amyloidosis. However, not all amyloidogenic precursor protein is deposited in the heart and exacerbates cardiac function. In the clinical setting, cardiologists mainly encounter 2 types of amyloidosis including, (1) amyloid light-chain (AL) amyloidosis and (2) transthyretin amyloidosis (ATTR).

AL amyloidosis

AL amyloidosis is caused by deposition of amyloid fibril derived from misfolded light chain of monoclonal immune globulin generated from abnormal plasma cells. The underlining diseases include multiple myeloma, primary macro gamma globulinemia, or monoclonal gammopathy of undermined significance. Cardiac involvement is the most important prognostic determinant. Mean age of onset varies depending on the underlining hematologic diseases, but usually younger than ATTR-related cardiomyopathy (ATTR-CM) [4].

If a patient shows rapidly progressing HF with left ventricular hypertrophy, the physician should suspect CA due to AL amyloidosis. Characteristics on concomitant physical examination, such as spleno-hepatomegaly, macroglossia, and polyneuropathy are sometimes observed and give us a clue of amyloidosis. In addition, the presence of serum monoclonal protein and urinary Bence Jones protein are highly suggestive for AL amyloidosis. But even if these biochemical markers are negative, we cannot rule out AL amyloidosis because of the limitation of sensitivity of these analyses.

Analysis of serum free light chain (FLC) is recommended for diagnosis and follow up of the treatment response in AL amyloidosis patients. The principal of the FLC analysis is that antibody against hidden surface of light chain detects serum FLC specifically. These characteristics enhance detection sensitivity much more than previous methods. Serum FLC levels are also a useful prognostic marker in patients with AL amyloidosis [5]. It should be noted that renal dysfunction influences FLC levels, and sometimes causes false positive results, especially in elderly patients. In that case, the ratio of FLC λ/κ might help the diagnosis because it is not affected by renal function and age.

In addition to these biochemical analyses, Congo-red staining and immunohistochemistry for light chain in tissue biopsy samples are necessary to determine therapeutic strategy. Diagnosis of CA is acceptable without performing endomyocardial biopsy, if a patient shows positive staining for amyloid fibril in involved tissue and displays characteristic structural and functional changes that are compatible with CA in echocardiography and cardiac magnetic resonance (CMR) imaging. In the case of negative Congo-red staining in involved tissue or abdominal fat, endomyocardial biopsy should be considered for diagnosis of CA. A patient whose tissue samples are negative for amyloid deposition is out of indication for chemotherapy, even if they show elevated FLC in their serum. Diagnosis flowchart of AL amyloidosis-related CA is shown in Fig. 1.

Transthyretin amyloidosis

TTR, also known as pre-albumin, is named from its function that it binds and transfers thyroid hormone and retinol-binding protein

Table 1
Classification of systemic amyloidosis.

Subtype	Amyloidogenic protein	Precursor protein	Organ involvements	Associated diseases
1. Primary amyloidosis				
1. AL amyloidosis	AL	Light chain (λ,κ)	Neuron, heart, kidneys, intestinal tract, skin	Plasma cell dyscrasias
2. AH amyloidosis	AH	Ig γ		
2. Secondary amyloidosis	AA	Apo AA	Intestinal tract, kidneys	Chronic inflammation, rheumatic arthritis
3. Hereditary (familial) amyloidosis (FAP)				
1. FAP I	ATTR	Mutated-TTR	Peripheral and autonomic nerve, heart	
2. FAP II	ATTR	Mutated-TTR		
3. FAP III	AApoA1	ApoA1		
4. FAP IV	AGel1	Gelsolin		
5. Familial Mediterranean fever AA	Apo SAA			
6. Muckle–Wells syndrome	AA	Apo SAA	Liver, spleen, kidneys	
4. Dialysis amyloidosis	Aβ2M	β2-microglobrin	Synovium, joints, tendon sheaths	End stage renal diseases
5. Senile systemic amyloidosis	ATTR	Wild type-TTR	Heart, tendon sheaths	Senility

Abbreviations: AL, amyloid-light chain; AH, amyloid-heavy chain; AA, amyloid A; FAP, familial amyloid polyneuropathy; ATTR, transthyretin amyloidosis; AApoA1, ApoA1 amyloidosis; AGel1, Gelsolin 1 amyloidosis; SAA, serum amyloid A; Aβ2M, β2-microglobrin amyloidosis.

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