


With M-protein positive, could transthyretin amyrodosis be easily excluded? Not necessarily! Wild-type transthyretin amyrodosis with Waldenström's macroglobulinaemia: a case report

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Background

Generally, it is said that amyloid light-chain (AL) develops not only in multiple myeloma but also in Waldenström's macroglobulinemia. We experienced a case of M-protein positive and diagnosed as wild-type transthyretin amyrodosis (ATTRwt) accompanied with Waldenström's macroglobulinemia.

Case summary

The patient was 72-year-old male, and the main complaint was dyspnoea in April 2020 and visited a nearby doctor. He was introduced to the Department of Haematology at our hospital for high levels of serum immunoglobulin M, M-protein positivity, and cardiac hypertrophy with a suspect of AL amyloidosis. Duodenal mucosal biopsy and abdominal skin biopsy showed no amyloid deposits, and left iliac bone marrow biopsy diagnosed Waldenström's macroglobulinemia and with no amyloid, and Kumamoto criteria score 1. Last of all, ATTRwt was diagnosed for endocardial biopsy.

Discussion

This is a very rare case of ATTRwt with Waldenström's macroglobulinaemia.

Keywords

ATTR • Amyloidosis • Waldenström's macroglobulinaemia • M-protein • Case report

ESC Curriculum

6.1 Symptoms and signs of heart failure • 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy

Learning points

- In general, M-protein or free light chains are one of the key tests to distinguish amyloid light-chain (AL) and transthyretin amyrodosis (ATTR).
- ATTR can also exist in the case of clinical background which suggests AL amyloidosis such as Waldenström's macroglobulinaemia.

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Introduction

Amyloidosis refers to a group of diseases caused by the deposition of amyloids of an insoluble polymerized protein in the extracellular areas of tissues and organs.^{1,2} Systemic amyloidosis is caused by the circulation of amyloids in the bloodstream and their deposition to organs throughout the body. This category of amyloidosis includes amyloid light-chain (AL) amyloidosis, amyloid A (AA) protein amyloidosis, transthyretin amyloidosis (ATTR), dialysis-related amyloidosis, and other conditions. As described previously,³ amyloidosis in multiple myeloma and Waldenström's macroglobulinaemia are almost exclusively due to AL amyloidosis, which is an immunoglobulin M (IgM)-related disorder.⁴

Timeline

| | |
|--------------|---|
| April 2020 | Symptoms of cardiac failure such as dyspnoea, pleural effusion, and lower leg oedema were observed. The patient visited a nearby hospital. |
| May 27 2020 | M-protein and high levels of serum immunoglobulin M was confirmed, and the patient was referred to the Department of Haematology, our hospital. |
| June 1 2020 | Duodenal biopsy performed amyloid deposition. |
| June 3 2020 | Bone marrow biopsy performed. |
| June 10 2020 | Skin biopsy performed amyloid deposition. |
| June 15 2020 | Bone marrow biopsy showed no amyloid deposits; diagnosis of Waldenström's macroglobulinaemia and myocardial biopsy performed. |
| July 7 2020 | Diagnosed with transthyretin amyloidosis. |

Case presentation

The patient was a 72-year-old man who complained of dyspnoea. He had had this symptom since April 2020, but because this symptom worsened, he visited a nearby hospital. Cardiac hypertrophy with high serum IgM concentrations and mild anaemia were found, and AL amyloidosis was suspected. Therefore, the patient was referred to the Haematological Department of our hospital. He had no history of regular visits to medical institutions, and his previous doctor noted atrial fibrillation, a positive faecal occult blood result, and iron deficiency anaemia. He had been prescribed torasemide, vonoprazan-fumarate, apixaban, ferrous sodium citrate, and vitamin C and calcium pantothenate tablets by his previous doctor. These findings suggested cardiac amyloidosis and Waldenström's macroglobulinaemia. His family had no remarkable medical history. An initial examination showed the following: height, 163 cm; weight, 58.3 kg; body mass index, 21.94 kg/m²; blood pressure, 135/88 mmHg; pulse pressure, 141 beats/min (irregular), and percutaneous oxygen saturation, 96%. He had mild oedema, but there were no abnormalities in the chest or neurological findings. An electrocardiogram showed atrial fibrillation with a QRS waveform width of 96 ms, and a chest X-ray showed mild congestion and cardiac enlargement (see [Supplementary material online, Figure S1A and B](#)). His bloodwork showed a WBC count of $7.5 \times 10^9/l$, Platelet count of $25.3 \times 10^{10}/l$, a RBC count of $365 \times 10^{10}/l$, and Hematocrit (HCT) of 36.8%. Other measurements were as follows: Hemoglobin, 123 g/l; HCT, 36.8 L/L; Total Protein, 80 g/L; Albumin, 41 g/L; Total bilirubin, 18.8 umol/L; LDH, 104 IU/L; Blood urea nitrogen, 5.36 mmol/L; Creatinine, 103 umol/L; Calcium,

2.3 mmol/L; C-reactive protein, 7000 ug/L; Glucose, 5.8 mmol/L; HbA1c, 5.4%; N-terminal pro-brain natriuretic peptide, 2636 pg/ml; High sensitivity cardiac troponin T, 0.032 ng/mL; immunoglobulin (Ig) G, 1394 mg/dL; IgA, 112 mg/dL; and IgM, 1514 mg/dL. Additionally, serum immunoelectrophoresis was positive for Ig type M-protein, and a monoclonal increase in the κ chain was found. The Bence-Jones urinary protein test was also positive, and the involved protein was the κ chain (see [Supplementary material online, Figure S2](#)). The patient underwent a duodenal mucosal biopsy and abdominal skin biopsy as a less invasive histological approach, but no amyloid deposits were found (see [Supplementary material online, Figure S3](#)). A left iliac bone marrow biopsy was performed, which also showed no amyloid deposition, but it showed an increase in plasma cell-like lymphocytes of more than 10%, leading to the diagnosis of Waldenström's macroglobulinaemia (see [Supplementary material online, Figure S4](#)). He also had heart failure, and we needed to pathologically detect amyloid deposition to make a definitive diagnosis of systemic amyloidosis. Therefore, he was referred to the Department of Cardiovascular Medicine. Echocardiography showed concentric hypertrophy with a ventricular septal thickness of 11 mm, a left ventricular posterior wall thickness of 11 mm, a left ventricular end-diastolic diameter of 40 mm, a left ventricular mass index of 103 g/m², and a relative wall thickness of 0.55. Coronary angiography was performed to rule out coronary artery disease, but no clinically significant stenosis was observed. In addition, hypertensive heart disease, valvular disease, myocarditis, and congenital heart disease were not present in the patient's history, clinical course, or echocardiography. We considered that the acute exacerbation of heart failure with reduced ejection fraction was due to the underlying cardiomyopathy, which caused concentric hypertrophy and tachycardiac atrial fibrillation acting as an exacerbating factor. The Kumamoto criteria⁵ were 1 point based on the assumption of cardiomyopathy resulting from cardiac amyloidosis. At the time of presentation, neither cardiac magnetic resonance imaging nor ^{99m}Tc pyrophosphate scintigraphy (^{99m}Tc-PYP) was available in our hospital. Because amyloidosis could not be detected by the above-mentioned minimally invasive histological examination, examining the histology of cardiomyopathy including amyloidosis was necessary. Additionally, a myocardial biopsy was performed at the same time as coronary angiography. Biopsies from the right ventricular septum were positive for Congo red stain and showed apple-green birefringence on polarized light microscopy. TTR immunostaining was also performed at Kumamoto University. On the basis of positive results, he was diagnosed with ATTR (see [Supplementary material online, Figure S5](#)). A genetic analysis of TTR was also requested by Kumamoto University. The DNA sequence of TTR exons 1–4 was analysed, but no genetic change was found. Accordingly, the condition was diagnosed as ATTRwt. The patient had a CHADs2 score of 2, and administration of apixaban 10 mg/day was started. He also started torasemide sodium ferrous citrate and bisoprolol fumarate administration, and his atrial fibrillation immediately returned to a sinus rhythm. Although his heart failure could be controlled by medication, early introduction of tafamidis was considered because he met the requirements for that treatment.¹

Discussion

This case was initially referred to the Department of Haematology because of the presence of high serum IgM and M-protein concentrations and cardiac hypertrophy. Therefore, examinations were mainly performed with the suspicion of AL amyloidosis. If cardiac amyloidosis is suspected, as in the present case, it should be positively diagnosed according to the algorithm¹ of cardiac amyloidosis because the diagnosis is directly related to the treatment policy and prognosis. As reflected in the clinical algorithm for cardiac amyloidosis,¹ M-protein detection and ^{99m}Tc-PYP are important tools for diagnosing the subtypes of cardiac amyloidosis. However, the observations in this case occurred before ^{99m}Tc-PYP were available in our hospital. Red flag findings suggested

cardiac amyloidosis^{6,7,8} (older male cardiac insufficiency, conduction disturbance, thickening of the interventricular septum, and an increase in troponin concentrations by 1 point in the Kumamoto criteria; hs-cTnT concentrations ≥ 0.0308 ng/mL).⁵ Generally, skin, duodenal, and bone marrow biopsies are relatively minimally invasive. If our patient had AL amyloid, it should be highly detectable in these biopsies.¹ Therefore, we expected that the diagnosis of amyloidosis would be made without a myocardial biopsy. However, in this case, ATTRwt was the only pathological diagnosis made by myocardial biopsy in contrast to our expectation. We consider that this case to be a good educational example of the usefulness of a myocardial biopsy.

The absence of M-protein is one of the criteria for the diagnosis of ATTRwt.¹ Additionally, M-protein is one of the most important factors in differentiating ATTRwt from AL amyloidosis because it can be easily tested. The presence or absence of M-protein detection is described in the American Heart Association Guidelines.⁹ In contrast, as described in the Japanese Circulation Society guidelines,¹ ATTRwt is frequently combined with monoclonal gammopathy of undetermined significance (MGUS) as M-protein-positive cases (10–18%). A total of 39% of patients with ATTRwt have abnormal levels of the free light chain associated with MGUS.¹⁰ As reported by Singh *et al.*¹¹ 'it might be expected that some Waldenström's macroglobulinaemia patients with evidence of cardiac amyloidosis could have unrelated ATTRwt'. Additionally, in MGUS, 15–20% of patients have IgM subclasses, which progress most frequently to lymphoma or Waldenström's macroglobulinaemia.¹² Therefore, we consider that there may be cases where MGUS with ATTRwt progresses to show Waldenström's macroglobulinaemia. However, further research on these cases is required. The number of diagnostic occasions for cardiac amyloidosis is likely to increase in the future. Therefore, cases such as our case, in which identifying the subtype of cardiac amyloidosis is difficult, are also likely to increase. Because AL amyloidosis and ATTR differ in their appropriate treatment, making an accurate diagnosis and not hesitating to conduct a myocardial biopsy are essential.

Conclusion

AL amyloidosis was suspected in this case because of heart failure with M-protein positivity and high serum IgM concentrations. Our patient had ATTRwt with Waldenström's macroglobulinaemia.

Lead author biography



Haruyuki Kinoshita was born in Kure, Japan in 1976. He worked at Fukui Prefectural Hospital, Rinku General Medical Center, and Ishikawa Prefectural Central Hospital and has been a clinician in the emergency and cardiovascular fields at the Kure Medical Center since 2012.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

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Data availability

The data underlying this article are available in doi (<https://doi.org/10.1093/ehjcr/ytac414>).

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