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Case Report

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Misdiagnosed light chain cardiac amyloidosis ultimately confirmed as hereditary transthyretin amyloidosis: a case report

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Abstract

Background: Cardiac amyloidosis (CA) diagnostic pathways are often complicated by the coexistence of monoclonal gammopathy of undetermined significance (MGUS) and transthyretin deposits (ATTR), especially in older populations.

Case presentation: A 73-year-old female presented with progressive heart failure. Initial screening revealed a monoclonal kappa-type immunoglobulin, and a Congo-red-positive abdominal fat pad biopsy further supported the suspicion. A diagnosis of light-chain (AL) cardiac amyloidosis was made, and the daratumumab-based chemotherapy was initiated accordingly. 99mTc-pyrophosphate scintigraphy also revealed myocardial tracer uptake, raising the possibility of transthyretin (ATTR) cardiac amyloidosis. Although coexisting AL and ATTR cardiac amyloidosis was considered, subsequent identification of a heterozygous TTR p.V142A mutation, along with proteomic confirmation by mass spectrometry (MS) of endomyocardial tissue, ultimately revised the diagnosis to hereditary ATTR (ATTRv).

Conclusion: This case underscores the diagnostic fallacy of relying on indirect biomarkers. Definitive amyloid typing—ideally via laser microdissection coupled with MS—is mandatory when serologic and scintigraphic findings are discordant.

Keywords: cardiac amyloidosis, monoclonal gammopathy of undetermined significance, light-chain (AL) amyloidosis, transthyretin (ATTR) amyloidosis, diagnosis, treatment

Introduction

Cardiac amyloidosis is a restrictive cardiomyopathy caused by the deposition of misfolded amyloid fibrils outside myocardial cells. There are two major subtypes, light-chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis. Transthyretin amyloidosis is further divided into variant transthyretin amyloid cardiomyopathy (ATTRv-CA) and wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CA)[1]. There are significant differences in diagnosis and treatment between AL amyloidosis and ATTR amyloidosis. Accurate molecular subtyping, along with further clarification of the precursor protein type, is essential for determining patient prognosis[2].

Diagnostic confusion may occur when monoclonal gammopathy is detected in a patient with suspected cardiac amyloidosis, particularly if bone scintigraphy is also positive. However, monoclonal proteins are not specific to AL amyloidosis, as they can also co-occur with ATTR, especially in elderly patients[3]. Here we report a case initially misdiagnosed as AL cardiac amyloidosis, ultimately confirmed as hereditary ATTR cardiac amyloidosis by endomyocardial biopsy and mass spectrometry.

Case presentation

A 73-year-old woman was admitted because of a 2-year history of progressive chest tightness and dyspnea, which had worsened over the previous month, and a 1-week history of abnormal immunofixation electrophoresis results. She had been diagnosed with chronic heart failure 2 years earlier at a local hospital. Despite regular treatment, she developed worsening orthopnea and bilateral lower-

extremity edema 1 month before admission.

Her medical history included hypertension for 25 years and hypothyroidism. She had undergone coronary stent implantation for an acute anteroseptal myocardial infarction in October 2024 and radiofrequency ablation for frequent premature ventricular contractions.

Electrocardiography showed sinus rhythm, low-voltage limb leads, and evidence of an old anteroseptal myocardial infarction（Figure 1）. Cardiac magnetic resonance imaging demonstrated cardiomegaly, right atrial enlargement, segmental left ventricular wall thickening, reduced global left ventricular systolic function, and diffuse transmural late gadolinium enhancement involving both the atria and ventricles, strongly suggesting cardiac amyloidosis（Figure 2）.

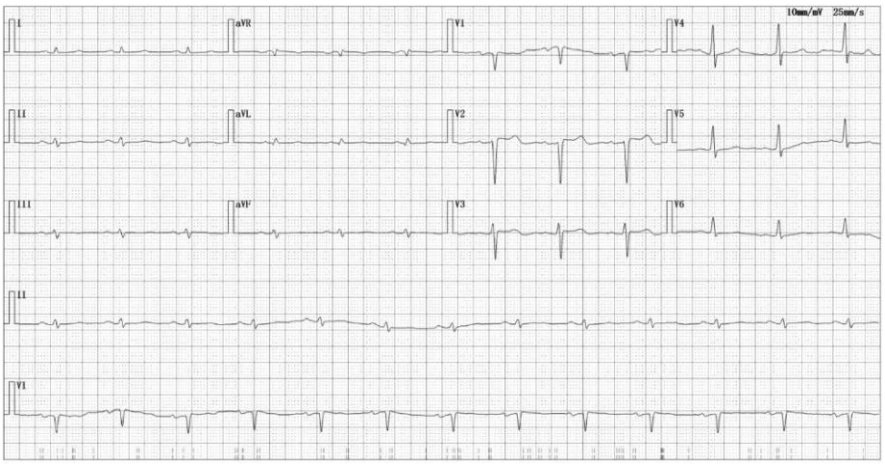


Figure 1 Electrocardiography showed sinus rhythm, low-voltage limb leads, and evidence of an old anteroseptal myocardial infarction.

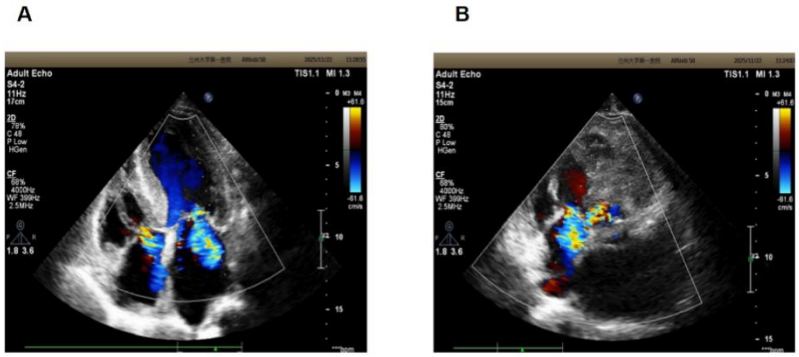


Figure 2 Cardiac magnetic resonance imaging demonstrated cardiomegaly, right atrial enlargement, segmental left ventricular wall thickening, and reduced global left ventricular systolic function.

Serum and urine immunofixation electrophoresis detected a monoclonal kappa-type immunoglobulin. Bone marrow examination showed a hypocellular marrow, with plasma cells accounting for approximately 0.8% of nucleated cells (Figure 3). To further evaluate for systemic amyloidosis, an abdominal fat pad biopsy was performed. Congo red staining revealed amyloid deposition with apple-green birefringence under polarized light (Figure 4). However, the precursor protein was not further characterized by immunohistochemistry or other amyloid typing methods at that time. Based on the available findings, AL cardiac amyloidosis was initially diagnosed.

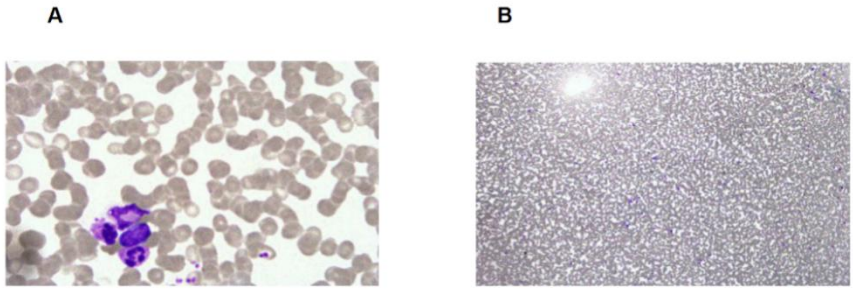


Figure 3 (A) Bone marrow examination showed plasma cells accounting for approximately 0.8% of nucleated cells (high-power field). (B) Bone marrow examination showed hypocellular marrow (low-power field).

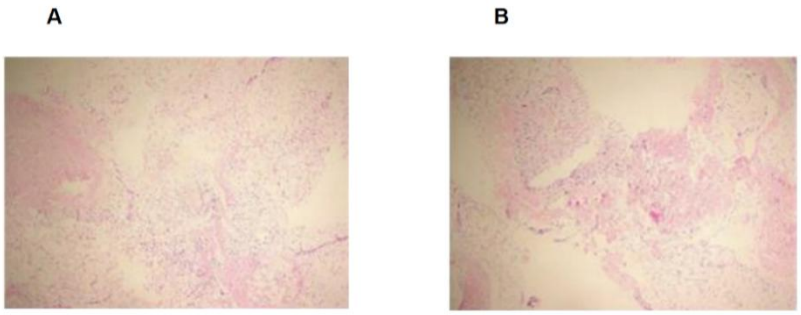


Figure 4 Abdominal fat pad biopsy. (A) High-power view with HE staining, showing fibrofatty tissue with fibrous hyperplasia and scattered homogeneous eosinophilic amorphous stromal deposits. (B) High-power view with Congo red special staining, positive staining of deposits confirms amyloidosis.

Given her history of hand symptoms, a neurological consultation and electromyography were obtained. The results suggested left median neuropathy at the wrist, consistent with carpal tunnel syndrome. Given the possibility of transthyretin amyloidosis, 99mTc-pyrophosphate scintigraphy (Figure 5) and peripheral blood TTR gene testing were subsequently performed. The scintigraphy showed myocardial tracer uptake. At that stage, coexistence of AL and ATTR cardiac amyloidosis was considered, and treatment with daratumumab, bortezomib, cyclophosphamide, and dexamethasone was initiated while awaiting genetic results.

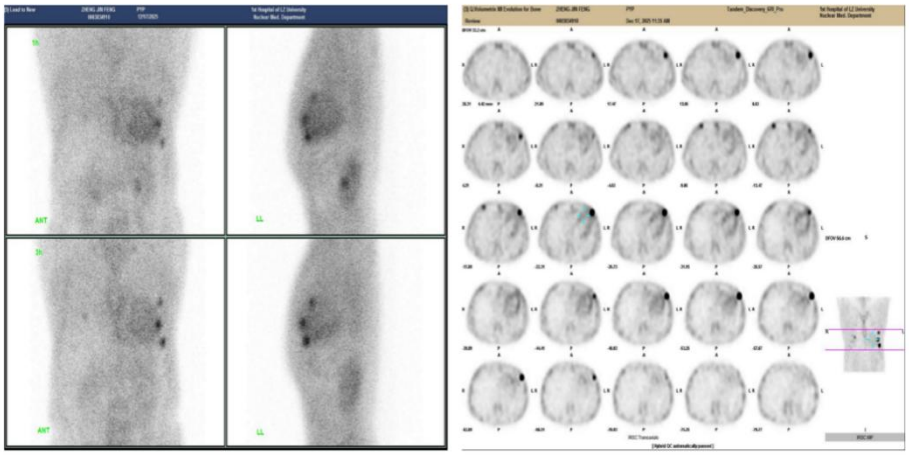


Figure 5 99mTc-pyrophosphate scintigraphy showed grade 3 cardiac uptake.

After discharge, genetic testing subsequently confirmed a heterozygous TTR mutation in exon 4

(c.425T>C, p.V142A)（Figure 6）. To confirm the amyloid subtype, endomyocardial biopsy was performed (Figure 7). Mass spectrometry revealed that the deposited amyloid was transthyretin-derived, with no evidence of immunoglobulin light-chain peptides（Figure 8）. The final diagnosis was hereditary transthyretin (ATTRv) cardiac amyloidosis. Tafamidis was initiated thereafter. Family screening was subsequently performed, which identified the same heterozygous TTR mutation in the patient's younger sister (the fourth of the sisters) on peripheral blood testing (Figure 9). This familial segregation further supported the diagnosis of hereditary transthyretin amyloidosis.

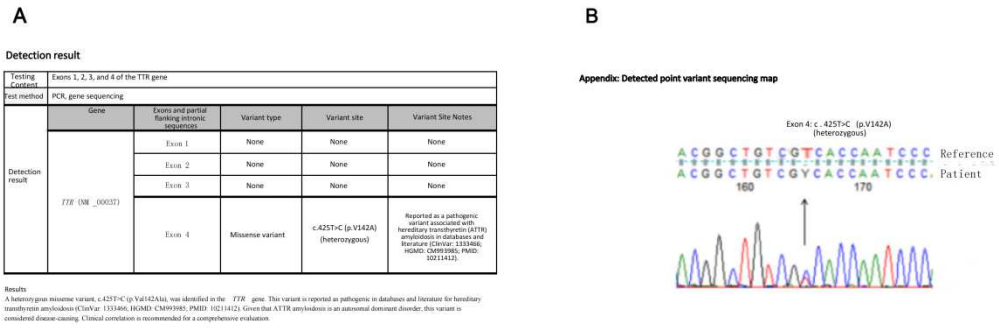


Figure 6 (A) Peripheral blood TTR gene testing showed a heterozygous TTR mutation in exon 4 (c.425T>C, p.V142A). (B) Sequencing chromatogram of the identified point mutation.

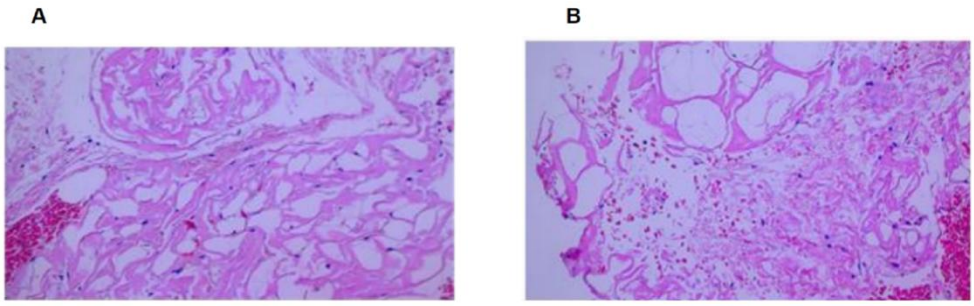
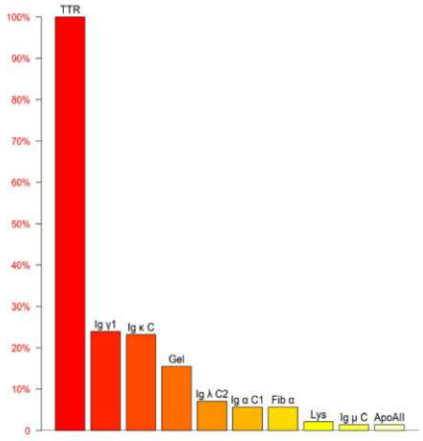


Figure 7 Endomyocardial biopsy. (A) HE staining shows interstitial adipose tissue, fibrosis, and focal homogeneous eosinophilic amyloid deposits. (B) Congo red special staining reveals positive amyloid deposits, consistent with amyloid cardiomyopathy.



	Identified Proteins	#spectra
•	Apolipoprotein A-IV	87
•	Apolipoprotein E	81
•	Serum amyloid P-component	30
•	Apolipoprotein A-I	23
1	Transthyretin	142
2	Immunoglobulin gamma-1 heavy chain	34
3	Immunoglobulin kappa constant	33
4	Gelsolin	22
5	Immunoglobulin lambda constant 2	10
6	Immunoglobulin heavy constant alpha 1	8
7	Fibrinogen alpha chain	8
8	Lysozyme C	3
9	Immunoglobulin heavy constant mu	2
10	Apolipoprotein A-II	2
11	Apolipoprotein C-III	1
12	Leukocyte cell-derived chemotaxin-2	0
13	Serum amyloid A-1 protein	0
14	Cystatin-C	0
15	Apolipoprotein C-II	0
16	Beta-2-microglobulin	0

Figure 8 Mass spectrometry typing showed that the deposited amyloid was derived from transthyretin, with no evidence of immunoglobulin light-chain peptides.

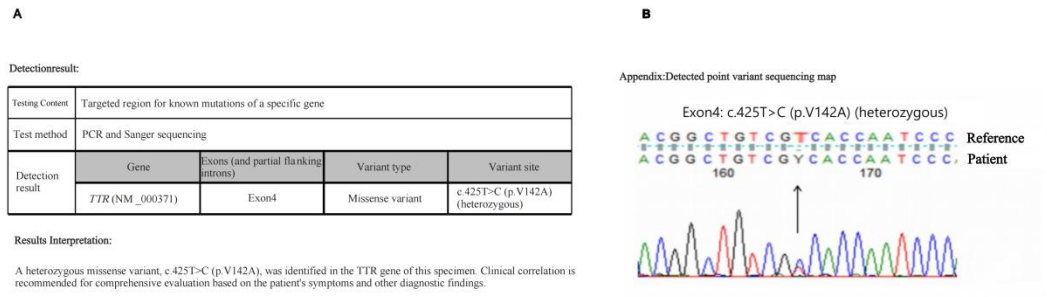


Figure 9 Family screening. (A) The patient's younger sister, who was the fourth of five sisters, was also found to carry the same heterozygous TTR mutation in peripheral blood. (B) Sequencing chromatogram of the identified point mutation.

Discussion

This case illustrates the diagnostic complexity of cardiac amyloidosis and the risk of misclassification when monoclonal gammopathy and ATTR-CA coexist. In this patient, the presence of a monoclonal kappa immunoglobulin, positive Congo red staining on fat pad biopsy, and a positive 99mTc-pyrophosphate scan led clinicians to favor AL cardiac amyloidosis and even to consider possible overlap with ATTR. However, none of these findings alone is sufficient to establish the type of precursor protein [2].

The primary diagnostic pitfall in this case stems from the high prevalence of MGUS among older adults with ATTR. A prospective cohort study by Phulla et al. (n=226) reported a high prevalence of MGUS in biopsy-proven ATTR amyloidosis, affecting 39% of patients with ATTRwt and 49% of those with ATTR V122I. These findings suggest that the presence of monoclonal proteins should not be equated with AL amyloidosis[4]. Here, the presence of a monoclonal kappa chain led clinicians to prioritize AL amyloidosis, despite clinical–pathologic discordance: severe cardiac amyloidosis contrasted with a minimal bone marrow plasma cell burden (0.8%). In patients with AL amyloidosis, the median bone marrow plasma cell percentage is 10% (IQR, 7%–20%) [5,6]. Thus, the 0.8% ratio differs significantly from the median, and this mismatch and low-burden feature should have triggered immediate caution before initiating chemotherapy.

Because endomyocardial biopsy can cause serious complications, considering the patient's advanced age and poor compliance, abdominal adipose tissue biopsy was first performed. However, Quarta et al. reported that the diagnostic sensitivity of abdominal fat pad biopsy in transthyretin cardiac amyloidosis (particularly ATTRwt) was low, ranging from 15% to 45%[7]. Congo red positivity merely confirms amyloid deposition, not its precursor. In this case, a positive fat pad biopsy falsely reinforced the diagnosis of AL amyloidosis, exemplifying the risk of overreliance on non-specific histology.

Electromyography indicated electrophysiological damage of the left median nerve at the wrist. Therefore, 99mTc-PYP scintigraphy was performed, and the result was positive. Taking into account the clinical symptoms, the doctor suspected that the patient was suffering from both AL-CA and ATTR-CA (which is itself an extremely rare condition[8]), and arranged for a peripheral blood TTR gene test. The TTR mutation c.425T>C (p.V142A) identified in this patient supports the diagnosis of hereditary ATTR amyloidosis. Endomyocardial biopsy combined with mass spectrometry was subsequently performed.

The results confirmed that the amyloid protein deposited in the myocardial tissue was derived from transthyretin (TTR). Ultimately, the patient was finally diagnosed with variant ATTR cardiac amyloidosis (ATTRv). Treatment with tafamidis, a TTR stabilizer, was initiated immediately. Subsequently, the patient's four sisters and one daughter underwent a family history investigation. We identified the same c.425T>C (p.V142A) gene mutation in the TTR gene test of its fourth sister. The TTR c.425T>C (p.V142A) mutation is a rare pathogenic missense variant associated with ATTRv. It shows autosomal dominant inheritance and typically presents with late-onset mixed neurologic and cardiac amyloidosis. Notably, this mutation is uncommon in the Chinese population. In the Chinese population, the most common TTR mutations are V30M and A97S, whereas p.V142A has been reported only sporadically in Asia and remains extremely rare worldwide[9,10]. Such a family history investigation is not only helpful for confirming pathogenicity but also important for early diagnosis and counseling of asymptomatic relatives.

Conclusion

When evaluating suspected cardiac amyloidosis, the coexistence of monoclonal gammopathy and ATTR-CA can easily lead to misdiagnosis. Congo red positivity and serum or urine immunofixation confirm amyloid deposition but do not determine the amyloid subtype. In ambiguous cases, biopsy of the affected organ with amyloid typing, preferably by mass spectrometry, remains the gold standard for diagnosis. Early and accurate subtyping is critical, as treatment strategies for AL and ATTR cardiac amyloidosis differ substantially.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The First Hospital of Lanzhou University (Approval No. LDYYLL

2026-899). Written informed consent to participate was obtained from the patient.

Consent for Publication

Written informed consent for the publication of this case report and any accompanying images was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of Interest

The authors declare that there are no conflicts of interest relevant to this work.

Data availability statement

No datasets were generated or analysed during the current study.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Contributor Role Taxonomy (CRediT): WY: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. LC: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – review & editing. XY: Supervision, Validation, Writing – review & editing.

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