HIDDEN IN PLAIN SIGHT

SUSPECT ATTR-CM

The diagnosis of ATTR-CM is often delayed or missed. Routine heart failure assessments such as echo and ECG, along with advanced imaging techniques, can help identify clues on the diagnostic pathway. By increasing your suspicion of ATTR-CM, you can identify patients who may require further testing to make a diagnosis.[1-3]

CONSIDER THE FOLLOWING CLINICAL CLUES, ESPECIALLY IN COMBINATION, TO RAISE SUSPICION FOR ATTR-CM AND THE NEED FOR FURTHER TESTING

HFpEF heart failure with preserved ejection fraction in patients typically over 60[4-6]

INTOLERANCE to standard HF therapies, ie, ACEi/ARB and beta blockers[1,3,7]

DISCORDANCE between QRS voltage and left ventricular (LV) wall thickness[8-10]

DIAGNOSIS of carpal tunnel syndrome or lumbar spinal stenosis[3,11-18]

ECHO showing increased LV wall thickness[5,10,18-20]

NERVOUS SYSTEM — autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss[5,18,21,22]

HFpEF: heart failure with preserved ejection fraction in patients typically over 60[4-6]

- In ATTR-CM, diastolic function is impaired due to amyloid fibril deposition in the myocardium resulting in thicker and inelastic ventricles, thereby decreasing stroke volume. It is not until the later stages of ATTR-CM disease that ejection fraction drops[23-25]
- Imaging clues, such as longitudinal strain with apical sparing, may help increase suspicion[1,23]

INTOLERANCE: to standard HF therapies, ie, ACEi/ARBs and beta blockers[1,3,7]

- Patients can develop a decrease in stroke volume, which can lead to low blood pressure. As a result, they can develop an intolerance to blood pressure–lowering therapies[3,7]

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

DISCORDANCE: between QRS voltage and left ventricular (LV) wall thickness[8-10]

- The classic ECG feature of ATTR-CM is a discordance between QRS voltage and LV mass ratio[1,9,26]
- The amplitude of the QRS voltage is not reflective of the increased LV wall thickness, because the increase is due to extracellular amyloid protein deposition rather than myocyte hypertrophy[1]
  - Absence of a low QRS voltage does not, however, rule out amyloidosis, as low voltage can vary among cardiac amyloidosis etiologies[5,9,10,12,27]

ECG and echocardiography images showing discordance of limb lead QRS voltages and the degree of LV wall thickness in a patient with cardiac amyloidosis[28]

Adapted by permission from BMJ Publishing Group Limited. [*Heart*, Grogan M, Dispenzieri A, Gertz MA, 103, 1065-1072, 2017]

DIAGNOSIS: of carpal tunnel syndrome or lumbar spinal stenosis[3,11-18]

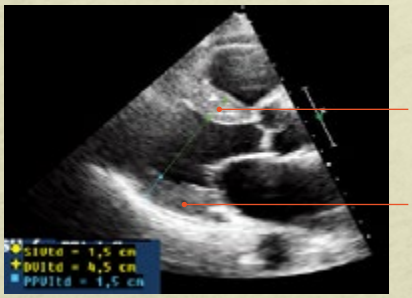
- Bilateral carpal tunnel syndrome and lumbar stenosis are often seen in ATTR-CM due to amyloid deposition in these areas [3,11-18]
- Bilateral carpal tunnel syndrome in ATTR-CM often precedes cardiac manifestations by several years[13,29,30]

ECHOCARDIOGRAPHY: showing increased LV wall thickness[5,10,18-20]

- Increased wall thickness without a clear explanation (ie, hypertension) should raise suspicion for cardiac amyloidosis[1,2]
- Extracellular amyloid deposition results in an increased LV wall thickness that tends to be greater in ATTR-CM than in AL cardiac amyloidosis, with reported thicknesses for ATTR-CM often being over 15 mm[9,10,18,20]

Transthoracic echocardiograms showing increased LV wall thickness

Parasternal long-axis view[4]



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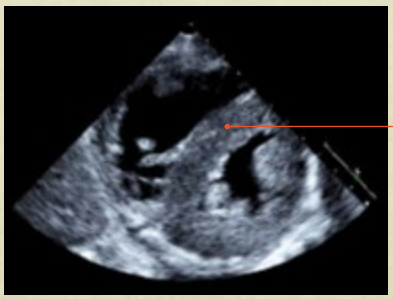
Parasternal short-axis view[23]



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NERVOUS SYSTEM: autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss[5,18,21,22]

- Gastrointestinal complaints due to autonomic dysfunction include diarrhea and constipation[31]
- Orthostatic hypotension due to autonomic dysfunction is another symptom that may occur with ATTR-CM[5,18,21]

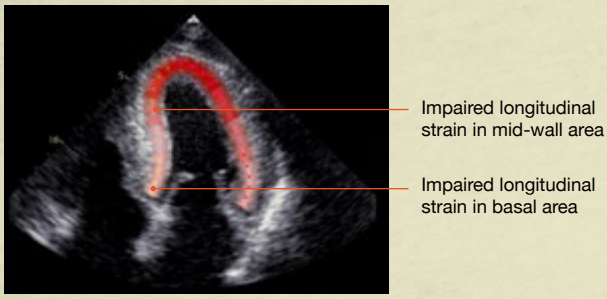
ADDITIONAL KEY CONSIDERATIONS

There are several additional signs/symptoms that could be clues for cardiac amyloidosis and ATTR-CM, which include:

- **Strain imaging showing apical sparing or apical preservation[1,2,10,20,23]**
  - Longitudinal strain seen on echocardiography is reduced in the basal and midwall area; however, the apical strain is spared or preserved[1,2,10,20,23]
- A history of bicep tendon rupture[31,32]
- A diagnosis of hypertrophic cardiomyopathy[1,2,33]
- Arrhythmias such as atrial fibrillation (most common) or other conduction abnormalities, which may require a pacemaker[4,5,12,34]
- Aortic stenosis and transthyretin cardiac amyloidosis may occur in elderly patients, notably those with a low-flow, low-gradient AS pattern[35-37]
- Hip and knee arthroplasty[38]

Examples of Strain Imaging Showing Apical Sparing

Apical preservation of longitudinal strain (commonly referred to as apical sparing)[1]



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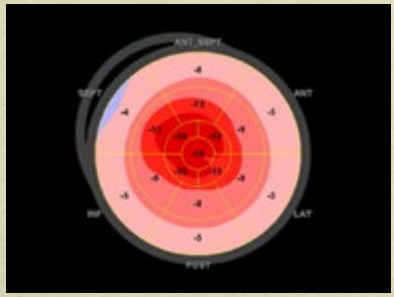
Bull's-eye plot of longitudinal strain showing apical sparing. This is often referred to as a "cherry on top" pattern[1]



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