DR. MARTHA GROGAN: Hi, I'm Martha Grogan, a cardiologist at the Mayo Clinic in Rochester, Minnesota. And today we'll review cardiac amyloidosis-- what every cardiologist needs to know. I have no disclosures pertinent to this presentation. So amyloidosis is really a fascinating disorder of protein misfolding. And there are over 20 different proteins that can form amyloid fibrils, but fortunately for us as cardiologists, only three of those really deposit in the heart. So we'll review the three most important types of amyloidosis that can cause cardiac involvement.

AL, previously called primary systemic amyloidosis, is a disorder of monoclonal light chains due to a plasma cell disorder. So the proteins are produced in the bone marrow. Familial amyloidosis is due to mutations in the transthyretin protein, and that's made in the liver. And the unstable, mutant version of this protein deposits to form amyloid fibrils in the tissues and organs.

And senile cardiac amyloidosis is also due to transthyretin deposition. But in this case, there's no mutation, and the molecule is actually structurally normal. But for reasons that really aren't clear, it deposits it within organs and tissues throughout the body. And again, it's made in the liver, same as patients who have familial amyloidosis. So what about cardiac involvement? AL amyloidosis, if one does a cardiac biopsy, it will be positive in almost all cases.

But the significance is of variable importance. In transthyretin cardiac amyloidosis, the familial type, the cardiac deposition varies tremendously with mutations. So some forms, the phenotype is almost exclusively neuropathy, where others are almost exclusively cardiomyopathy. And senile cardiac amyloidosis, which again, is also due to transthyretin amyloidosis, is almost always isolated to the heart, other than the association with carpal tunnel syndrome.

And this, for reasons that really are not clear, almost always occurs in elderly males. So why is it so challenging to diagnose cardiac amyloidosis? Well, first of all, the symptoms are often vague, and they can be common and overlap with many of our other diseases. So patients often present with exertional dyspnea, fatigue, chest pain. They can even present with acute coronary syndrome. They may have valvular heart disease. Atrial fibrillation is a common manifestation, particularly in patients with senile amyloidosis.

Syncope, stroke, and conduction system disease all may occur. And many times, patients, by the time they get diagnosed and present to a cardiologist, have developed overt heart failure. So delayed diagnosis is really a major factor in poor prognosis. And as cardiologists, we really need to try to make the diagnosis earlier. So what are some of the clues that should really cause you to think about the diagnosis of cardiac amyloidosis?

Well, first of all, if you have a patient with a dyspnea or heart failure, who has unexplained weight loss, peripheral or autonomic neuropathy, unexplained hepatomegaly, nephrotic syndrome-- all of those things will make you think of cardiac amyloidosis. Well, here's a patient who presented when she was 55 years old with exertional dyspnea for the past two years.

And I'm going to tell you right off the bat that she has cardiac amyloidosis, but if you look at her echo, it doesn't look at all like what we would usually think to be cardiac amyloidosis. So her wall thicknesses are normal. She has reduced left ventricular rejection fraction, and her right ventricular wall thickness were normal. But she did have some other clues to the diagnosis, and that was that her ECG showed a new, pseudo-infarct pattern, an anteroseptal infarct pattern, although there were no regional wall motion [INAUDIBLE] on Echo.

And she had new low voltage. Her 24-hour urine showed proteinuria. She was hypotensive with exercise. And then, to top it all off, she was going home to get a carpal tunnel release that had already been scheduled. So this patient had a lot of clinical clues to cardiac amyloidosis, even though her echo does not at all show us typical findings.

So if you're the clinician, I want you just to think to yourself, what would you order? What tests would you order to try to establish the diagnosis? And sometimes that's a little bit confusing, but the important thing to remember is that you need to do a serum and urine immunoelectrophoresis, sometimes called monoclonal protein studies-- not just a plain serum protein electrophoresis, because that can miss the monoclonal protein. And importantly, we now also have serum-free light chains, which are widely available.

And if you do both of those things, serum and urine immunoelectrophoresis as well as serum-free light chains, you'll pick up 95% to 100% of the AL type of amyloid. Tissue diagnosis is mandatory in the diagnosis of cardiac amyloidosis. So once you suspect the disorder, even if you have abnormal monoclonal proteins and serum-free light chains, you have to get a tissue specimen from somewhere.

Most commonly we use a fat aspirate as a screening tool, and that will pick up the majority of patients with AL amyloid. But it's not as sensitive in the transthyretin cardiac amyloidosis-- only about 20% of patients with senile cardiac amyloid. So in those cases, you may need to do a cardiac biopsy. So again, you can use fat aspirate, the bone marrow, particularly in AL amyloid. And the importance is that you need to prove amyloid organ involvement and determine the type. Is this AL amyloid, or is it transthyretin cardiac amyloid?

And it's really fascinating that it's not all about wall thickening, because I showed you this patient who has normal wall thickness, but she had very severe heart failure due to cardiac amyloidosis, the AL type. And in fact, she underwent a heart transplant within six months. Yet one will see other patients, such as this. Here's a patient on the right side of your screen who's walking three miles a day despite really severe wall thickening. Septum measuring 28 millimeters or so.

And this is a patient with senile cardiac amyloidosis. So we need to realize what really causes organ dysfunction in amyloid. So we recognize that it is an infiltrative disorder, and here we see cardiac myocytes with amyloid fibrils and depositing in the extracellular space. So that's a traditional mechanism of infiltrative cardiomyopathy, and that's certainly an important cause of heart failure and symptoms in the majority of these patients.

So here we see that as more and more amyloid is deposited, the cardiac cells become distorted and displaced. However, it's interesting that direct toxicity of the light chains has been proposed and has been proven in animal models. So light chains and other pre-fibrillar proteins cause oxidative stress and probably contribute significantly to cardiac dysfunction in the AL type of amyloid. So here in this schematic, we see the cardiac myocytes and immunoglobulin proteins, with the light chains, if you think of this in just a schematic fashion, kind of directly attacking the cardiac myocytes.

And that probably explains for the patient that we saw with normal wall thickness having such severe heart failure. Interesting that the ECG, there is really not that much written about it in cardiac amyloidosis. In a series that we've reviewed here of 127 patients with biopsy-proven cardiac involvement, low voltage and pseudo-infarct pattern were the most common manifestations in AL amyloid. But notice that in transthyretin amyloid of the senile type, only 10% of patients had low voltage. So it's really important to recognize that distinction.

And ECG criteria for left ventricular hypertrophy was actually present in about 16% of patients who had AL amyloid. So normal voltage, or even LVH criteria, did not exclude the diagnosis of cardiac amyloidosis. Many of you recognize that cardiac MRI has really aided in the diagnosis of this disorder, due to diffuse late gadolinium enhancement and a characteristic pattern of difficulty nulling the myocardium.