Myocarditis - Advances in Diagnosis and Treatment

Announcer: Welcome to the Mayo Clinic Cardiovascular Continuing Medical Education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Bell: I'd like to welcome our viewers and listeners to another in our session of "Interviews with the Experts". My name's Malcolm Bell. I'm the Vice Chair for the Department of Cardiovascular Medicine here in Rochester. And I'm delighted to have my colleague and friend, Dr. Les Cooper join us today to talk about what's new in myocarditis, in terms of diagnosis and treatment. Les is a Professor of Medicine. He's the Chair of the Department of Cardiology in our sister site of Jacksonville in Florida. And he is a particular expert in myocarditis, all aspects, and recognized internationally for his expertise here. So welcome, Les.

Dr. Cooper: Malcolm, tank you so much. It's great to be with you today.

Dr. Bell: There's clearly a lot we can discuss about myocarditis, in terms of the epidemiology, presentation, diagnosis, treatment. But really just gonna focus on imaging and the treatment of this in our discussion today. So let's just start with the question of cardiac imaging. And we got a patient that we suspect may have myocarditis. And very routinely, echocardiography is used in this and in some patients where we're trying to rule out an acute myocardial infarction, cardioangiography may be performed in selected patients. But let's get back to the echo because it is routinely used in these patients. And so, what are we looking for there that would help us in the diagnosis of myocarditis?

Dr. Cooper: So beginning in the 1980s and 1990s, echocardiography was used widely to define myocarditis and other forms of cardiomyopathy. And it turned out that there are strong prognostic variables, including left and right ventricular ejection fraction, that predict major adverse cardiac events in myocarditis, as well as as many other forms of cardiomyopathy. However, there's not anything very specific on echocardiography for myocarditis. And that led in the late 1990s to the use of cardiac MRI, which could provide tissue characterization.

Dr. Bell: So you brought up cardiac MRI, and that's clearly something that we need to discuss. And I think our audience will be very interested in hearing. So what is the role for cardiac MRI in these patients? And maybe just start off saying, what are you looking for in cardiac MRI that's gonna help you in the diagnosis of someone with presumed or suspected myocarditis?

Dr. Cooper: Well, cardiac MRI has been evolving over the last two decades. We wrote the Lake Louise I criteria in 2009 and Lake Louise II in 2018 specifically looking for acute lymphocytic myocarditis. Generally, that's a postviral syndrome. And those criteria currently require both a T1 weighted, which would be like delayed enhancement, or a T2 weighted native mapping or imaging sequence to make the diagnosis of acute and presumed viral or idiopathic myocarditis. Of course, there are many other causes of myocarditis, most recently COVID and vaccine-associated myocarditis that we have been extrapolating from the original criteria to assume that those patterns of inflammation, generally epicardial and generally inferoposterior, are relevant to these novel mechanisms. I'd emphasize that genetic cardiomyopathies, such as desmoplakin or

plakophilin mutations, and those associated with cardiac sarcoid or giant cell myocarditis are a bit different than the routine findings we see in viral myocarditis.

Dr. Bell: The actual findings that on MRI, I mean you, you talked about some anatomical locations that might point to a specific cause. But what exactly are you looking for on the MRI images?

Dr. Cooper: In the acute setting, which would be less than two to three weeks from symptom onset, we look for a matched increase in water sensitive sequences, such as T2 mapping or bright white areas on T2 imaging, combined with an increase in delayed enhancement sequences. Generally, these are on the outside of the heart, the epicardium, which is different than with ischemia, which would be more on the endocardium and moving outward. So it is a distinct pattern for non-ischemic cardiomyopathy. And with the T2 weighted imaging, it's more specific for myocarditis. In fact, the area under the curve is greater than 90.9 for the combination of T1 and T2 weighted imaging.

Dr. Bell: So if we just stay with the acute presentation of myocarditis, what is the sensitivity and specificity of cardiac MRI in diagnosing myocarditis? You already talked about the lack of specificity with echo findings.

Dr. Cooper: They approach 90%. But that is only true in the first few weeks of illness. Once you get out beyond about one to three months, the signals return toward a baseline and the accuracy of cardiac MRI for acute myocarditis goes pretty far down. However, I would say the prognostic value of an MRI, I think remains true. And in addition to the ejection fraction, which you get on echo, the tissue area of delayed enhancement is prognostically important. It's been demonstrated in multiple studies for specific forms like cardiac sarcoid, for example, where you have higher degrees, greater than about 7% of the myocardium, is if it's involved with delayed enhancement, is associated with a greater risk of arrhythmias or heart failure.

Dr. Bell: Per chance, though then that we should be doing cardiac MRI routinely and anyone we are suspecting of acute myocarditis in that acute setting. It may be difficult to employ, of course, in someone with fulminant myocarditis, who's in intensive care on a ventilator. So presumably then we're looking for opportunities to do that in follow up. Is that generally your experience? And again, the recommendations for doing this routinely otherwise?

Dr. Cooper: That is correct. So all the current scientific papers, the position papers from the European and US literature recommend that in the setting of suspected acute myocarditis that's stable hemodynamically, not requiring mechanical circulatory support or inotropes, as you mentioned, or a ventilator, or lots of arrhythmias that you proceed with an MRI ideally within the first few weeks. On the other hand, if it is an unstable or fulminant presentation, where you're in the unit. You've got lots of ventricular arrhythmias. You've got instability, which would make the image acquisition less accurate and risky for the patient. In that setting, it's safer to go on toward biopsy, and then delay MRI until a time when it's feasible and safe.

Dr. Bell: That's a good segue into my next question and... Well, actually next two questions. So in terms of the findings that you... So let's say you don't have a patient who's got fulminant

myocarditis and is unstable in the intensive care, you do cardiac MRI, do you use that as a tool to guide who then you might want to perform endomyocardial biopsy? Or diagnosis gonna be sufficient from the clinical presentation and what you see on cardiac MRI?

Dr. Cooper: So the indications for biopsy are based upon clinical presentation and not upon imaging, specifically on MRI. For example, in a patient with an acute non-ischemic cardiomyopathy who has hemodynamic instability, meaning they're inotrope-dependent, or they need mechanical support, or they've got life-threatening ventricular arrhythmias, or high grade heart block, that is a class one indication for an endomyocardial biopsy. That has been since the 2007 Scientific Statement came out. And it remains in to this day. In addition, I think there are specific times, for example, if there is a uncertainty about myocarditis in the setting of checkpoint inhibitor therapy, where that's a very significant diagnosis, it would... The cancer treatment is often lifesaving. And withholding it could be, mean advanced cancer. That's where you really do need to know whether the diagnosis is correct. So there are a few specific circumstances outside of that fulminant hemodynamically unstable circumstance where you might want a biopsy.

Dr. Bell: So let's just stay on that fulminant unstable myocarditis patient for for a moment. So there's that patient in intensive care, who has just presented. They're in shock. Is there a role for immediate steroids before you've even taken the patient to the cath lab for a biopsy?

Dr. Cooper: Yep, that's a question that hasn't been answered in a rigorous way. Many of us would feel that a gram of Solu-Medrol is safe. And often on a weekend or an evening, it's not feasible to bring in a cath lab and get a Cardiac Pathologist. And so, we would proceed that way. However, that's being studied in a clinical trial called the MYTHS Trial. It is headed out of Milan, Italy. And they are enrolling sites currently in Spain, the Netherlands, and Italy in that multi-centered trial, which is looking at a gram of Solu-Medrol once a day for three days for fulminant myocarditis, randomized trial.

Dr. Bell: So let's move away from that patient who has fulminant myocarditis, the unstable patient. And someone who still... And again, I just wanna focus on the acute presentation, or it could be within that first or week or so. And in terms of diagnosis when you brought up the complication of checkpoint inhibitors and you mentioned giant cell myocarditis, what are gonna be the specific treatments you might offer for those? And I guess another disease would be sarcoid that you may pick up at some point?

Dr. Cooper: Absolutely, in the last decade, the immune checkpoint inhibitors, like nivolumab, for example, have taken a really important role in cancer therapy. A small percentage between one in 300 and one in 100 patients may get myocarditis as a consequence of downregulating T regulatory cell function. And that is very important because myocarditis in that setting has a high rate of serious heart failure, arrhythmias, and heart block with about a third mortality. And so in that setting, the clinical treatment depends on how severe the disease is. In those patients who have an asymptomatic increase in troponin, the recommendation from ASCO is to hold the treatment and recheck the troponin. It may be reasonable to re-challenge with the same or a different therapy. In those patients, in contrast, who are symptomatic, if they've got heart failure, if they've got clinically symptomatic arrhythmias, the recommendation is to proceed with Solu-

Medrol, a milligram per kilogram, one to two milligrams per kilogram, and then consider adding another agent. The sicker patients, those in the intensive care unit, who are developing high grade heart block, the recommendation is not only Solu-Medrol, but another agent, something like Abatacept.

Dr. Bell: And with giant cell myocarditis, what about those?

Dr. Cooper: Yep, so we've known since the late 1990s that calcineurin inhibitor therapy directed at T-cell inflammation is helpful in prolonging time to transplant or preventing death in patients with giant cell myocarditis. Those original studies were a bit confounded because muromonab-CD3 or OKT3 was used in a number of cases. And that is no longer available. The current recommendation for giant cell, which is biopsy proven, is to go with the same steroid regimen recommended for checkpoint inhibitor myocarditis, which is that gram of Solu-Medrol once a day for three days with a steroid taper, followed by a calcineurin inhibitor, like cyclosporine. And in addition, in the unstable patients, consider a third lytic agent, like anti-thymoglobulin or Campath.

Dr. Bell: In the past, I mean, in the last few decades, those studies are looking at treatment of, I mean, immunotherapy and just general, your myocarditis. I mean, rather disappointing. And so, when we get back to talking about your biopsies, we were looking for more than just sort of evidence of inflammation. And obviously, there's immunologic and immunohistochemical were things you should be looking for. So presumably, that's really led to a greater understanding of the inflammatory response in the heart.

Dr. Cooper: Yes.

Dr. Bell: But so, where are we now then with the treatment of, let's say, it looks like lymphocytic myocarditis in patients? I mean, obviously, we're still providing supportive care for heart failure and arrhythmias. But are there treatments available now, or on the horizon, or is that something that's still being studied?

Dr. Cooper: It is being studied. So going back to 1995 with the negative myocarditis treatment trial that showed that cyclosporine or azathioprine with steroids did not prolong, improve ejection fraction or prolong survival in patients with acute lymphocytic myocarditis. There was generally a lack of of studies for the next decade or so. The focus was on specific causes. And those today, which change management, are cardiac sarcoid in the right clinical context, giant cell myocarditis, checkpoint inhibitor myocarditis, or the drug reaction of eosinophilic myocarditis. Now, for lymphocytic myocarditis, that is an area under investigation. There are several ongoing clinical trials, one out of Canada by Cardiol Rx is studying pharmacologic grade CBD. Another is looking at specific monoclonal antibodies to prevent major adverse events in acute lymphocytic myocarditis. And that can be diagnosed by MRI or by biopsy in those studies.

Dr. Bell: Okay, well, this is really fascinating. Les, is there anything else you wanted to add before we close up here?

Dr. Cooper: No, I just encourage the audience to remain aware. We have updated information on the Myocarditis Foundation website. It's updated regularly, www.myocarditisfoundation.org. And please keep up with the literature. It's evolving quickly.

Dr. Bell: Yeah, I mean, I think it's very clear from this discussion here, there's been significant progress in understanding the mechanisms here. And you've highlighted a number of novel courses of myocarditis and specific treatments for that. And it seems though we could look forward to learning more about this, but particularly, getting more standardized regimens for for treatment of myocarditis. Really appreciate your time with us today, Les.

Dr. Cooper: Thank you.

Dr. Bell: And look forward to some more discussions on this in the future.

Dr. Cooper: It's great being with you, thank you so much.

Announcer: Thank you for joining us today. Feel free to share your thoughts and suggestions about the podcast by emailing cvselfstudy@mayo.edu. Be sure to subscribe to the Mayo Clinic Cardiovascular CME podcast on your favorite platform and tune in each week to explore today's most pressing cardiology topics with your colleagues at Mayo Clinic.