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Paul Collinson and Patrick Kiely.
Unexpected Troponin Elevation in a Patient Treated with Atorvastatin.
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Guest: Dr. Paul Collinson is a Professor of Cardiovascular Biomarkers and Honorary Consultant Cardiologist at St. George's University Hospitals NHS Foundation Trust and St. George's University of London.

Randye Kaye: Hello and welcome to this edition of "JALM Talk," from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Cardiac troponins T and I represent the current mainstay of diagnosis for myocardial infarction. These cardiac troponins are more specific to heart muscle rather than skeletal muscle relative to previous generations of cardiac biomarkers such as CK-MB. The more recent highly sensitive generations of troponin assays are thought to be particularly specific to cardiac muscle injury; however, potential interferences in patients with muscle pathologies may still exist.

A Case Report in the July 2020 issue of JALM describes a patient on statin therapy who presented with elevations in creatine kinase and cardiac troponin T, but who did not show cardiac symptoms. The first author of this report is Dr. Paul Collinson. Dr. Collinson is a Professor of Cardiovascular Biomarkers and Honorary Consultant Cardiologist at St. George's University Hospitals NHS Foundation Trust and St. George's University of London. Dr. Collinson is our guest for this podcast. Welcome, Dr. Collinson. Why did this patient come see you originally and what blood tests did you request at that time?

Dr. Paul Collinson: Okay. Well, I am a medically qualified clinical chemist, which is not that common in America, but it's not uncommon in Europe, which is where I'm from as you might have gathered. And this lady came to see me because my clinical specialty is in what is now known as preventive cardiology because I'm essentially a lipid specialist. Her problem was that she previously had a coronary artery bypass. She had been quite appropriately put on atorvastatin but she was having difficulty taking it. In fact, when she came to see me, what had happened was she had gone on holiday and she had driven from the airport to her hotel. When she got to her hotel, she couldn't actually get out of the car and she thought this was a little odd, not unreasonably.

So when she came to see me, I was specifically asked to review why she might be intolerant to statins. And so, I did

some baseline tests. I obviously checked her liver function, her renal function. I knew she was diabetic already. Because she had a muscle problem, I checked her CK and because we've had high-sensitivity troponin in the UK for really quite a long time and I know it relates to cardiovascular prognosis, I checked her high-sensitivity troponin as well.

Randye Kaye: Can you summarize the results of the blood tests? And were you surprised at them or did you think she could have a heart attack?

Dr. Paul Collinson: Well, basically most of her blood tests were unsurprising. Her renal function was normal. Her liver function was a little, little bit abnormal, but I knew she was a diabetic. Her CK, her creatine kinase was elevated at 2,853 and in our lab, we usually expect it to be below 200. Her troponin was also elevated at 55 and that caused me pause because the upper reference limit in our lab for troponin T is 14. But I looked at it and thought, well, I don't think this lady is likely to have had a coronary. She was extremely well in herself, she wasn't complaining of any cardiac symptoms. And one of the great things is patients who have had heart disease, they know what heart pain feels like. You and I think it's pain in the chest, but it's actually not. It's though as someone dropped a weight in your chest, and she had no symptoms at all. And I also knew that in people such as herself, who were less young than they used to be, that slightly elevated levels of troponin are in fact quite common. So, I wasn't concerned but I was a little bit surprised to see an elevated troponin at that point.

Randye Kaye: So these kind of suspicious results, what did you do next?

Dr. Paul Collinson: Well, obviously, there are sort of two aspects to it. I wasn't that surprised that she had an elevated CK because she did complain of symptoms of myositis. That being said, if you look in the literature and my clinical experience is much the same, most people who complain of statin-induced myopathy or statin-induced muscle pain in fact have entirely normal CKs, and if you look through the literature, it's not really a very good test. So what I thought to myself is, well, actually, this lady probably does have myositis because her CK is up.

The question then really was, why does she have an elevated troponin? So, the first thing to do was to deal with the why she had a myositis and for that I'm very fortunate at St. George's Hospital, I have an excellent colleague called Patrick Kiely, who is the co-author on this Case Report. He was particularly interested in fact in myositis and has had a lot of experience and I've referred him patients in the past. So, I obviously referred her to him. He is a very sensible chap. He arranged specialist autoantibody testing including a test

which I've never heard of, which was antibodies for HMG-CoA reductase.

Now, HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis and is the enzyme which statins are specifically targeted. I left that to him and I was really concerned about why might she have an elevated result from a laboratory point of view. So, the first thing I did was to check the cardiac troponin I. If it is a myocardial injury, then both cardiac troponin T and cardiac troponin I would be elevated, and the cardiac troponin I came back completely normal. It was in fact 5, which is which is very, very good.

So we did start doing some other tests. We checked to see whether there might be a heterophile antibody interfering. That wasn't the case. We screened for a presence of a macrotroponin. That came back negative. So we started scratching our heads at this point because clearly it was a true false-positive test, but it wasn't due to an assay interference.

Randye Kaye: So what was the final diagnosis and what was the cause of the elevated troponin?

Paul Collinson: Well, Patrick's antibody tests all came back and all the myositis-related antibodies were in fact negative. So that suggested that it didn't seem to be an autoimmune myositis from the point of view of it just being an autoimmune disease. However, the anti-HMG-CoA reductase antibodies came back as positive. So that said, actually what we were looking at here was a genuine statin-induced myositis, which is actually quite rare. That was very interesting. Obviously, we had taken her off all lipid-lowering drugs and the interesting thing was that after we did that, she started to feel much better. All her muscle aches went away, and interesting enough, her CK dropped down ultimately in fact to normal.

And as that happened, her troponin started to become negative, where it went down to essentially a normal value. So we first of all concluded that the final diagnosis must be a statin-induced myopathy. And then came the interesting question, why was the troponin elevated, and that's really quite interesting. We had excluded analytical interferences, but she did obviously have myositis and there was evidence of muscle injury and muscle regeneration. Now, this has been previously recorded and there was a lot of discussion in the early days of troponin, about troponin T not being sensitive when there was muscle injury.

I must confess I've always been a bit skeptical about this because there's a lot of troponin wars between the manufacturers. But essentially, here was a case right in front of my eyes where I can say, well, actually the only

explanation is this lady has got muscle regeneration and then I did actually find out that not only is this actually quite well-described in the rheumatology myositis literature, which is obviously quite specialized, but in fact there's recently been some molecular biology work confirming that in patients on statins who have myositis, there is expression of a cross-reacting isoform of troponin T, which it's not actually a cardiac troponin T, but it does cross-react in the assay. So essentially, what we're looking at here is a true biological false-positive; very rare, but genuinely exists.

Randye Kaye: All right, thank you. So just taking this forward to maybe this case has implications for interpretation of troponin results in other patients, can you summarize some key take-home points for our audience?

Paul Collinson: Well, I do this really wearing my two hats. First wearing my clinical hat, I would say to any clinician anywhere, if the laboratory tests don't fit the clinical picture, then you should be suspicious and especially talk to your laboratory colleagues.

And one of the things which is a sort of constant, I'd say, thorn in my side, but a disappointment, is that most labs don't get out there and talk to their clinicians and most clinicians don't get out there and talk to their labs. And I have known a very similar case where a patient came in with elevated troponin. It was found to be due to a true analytical false-positive this time, but the patient had multiple cardiac catheterizations in a desperate attempt to find out why the troponin was up before eventually one of the clinicians talked to the lab and they tracked it down.

The second really for my lab colleagues is that if you are alerted to something that looks a little suspicious, start investigating. Find out why it's there. The problem we have is we all live in our little silos and we don't talk to our colleagues, we don't interact with other disciplines. And I was quite surprised to find out the rheumatologists are sort of -- they consider troponin T to be a test for muscle and heart, and troponin I to be the heart test, which is intriguing. But when you talk to general physicians and cardiologists, they're much less aware of these type of findings. And of course my final take-home message is, you should explore your test results, but publish them in an excellent journal such as JALM.

Randye Kaye: Wonderful take-home points. Thank you so much. Thank you for joining us today, doctor.

Paul Collinson: Thank you.

Randye Kaye: That was Dr. Paul Collinson from St. George's University Hospitals NHS Foundation Trust describing his JALM Case

Report, "Unexpected Troponin Elevation in a Patient Treated with Atorvastatin."

Thanks for tuning in to this episode of "JALM Talk." See you next time and don't forget to submit something for us to talk about.