LEAP ROUNDS

Johns Hopkins University
School of Medicine
Division of Rheumatology
Fall 2023

Inclusion Body Myositis

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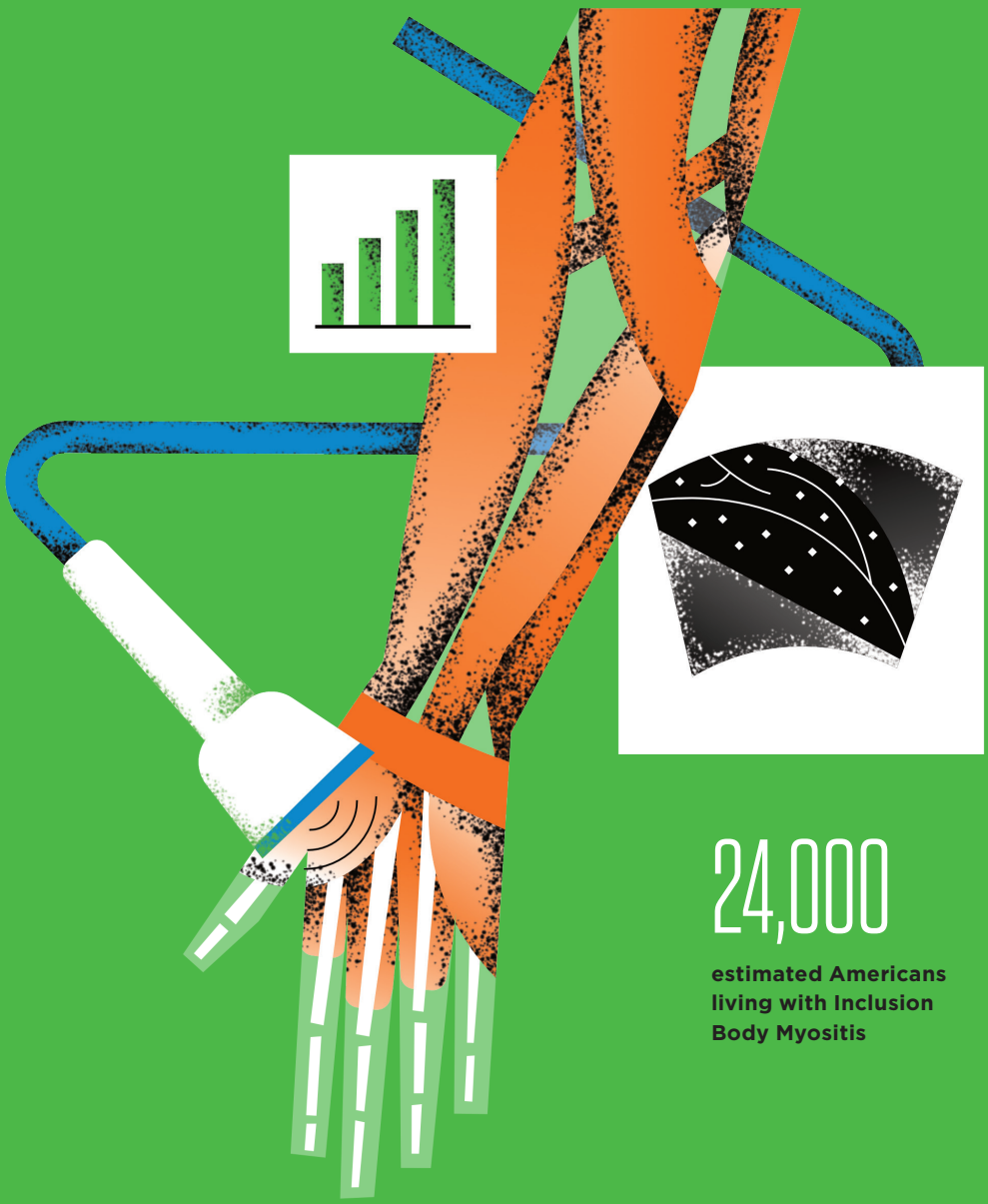
What's Really Happening in the Muscle?

INCLUSION BODY MYOSITIS



24,000

estimated Americans living with Inclusion Body Myositis

Never underestimate the body's ability to compensate. We have seen this in our patients with inclusion body myositis (IBM), thanks in part to musculoskeletal ultrasound, as part of a recent clinical trial we conducted at the Johns Hopkins Myositis Center.

Traditionally, MRI has been the imaging modality of choice when we are trying to decipher whether there's involvement and inflammation in the muscle. A couple of years ago, we began asking the question: can ultrasound also detect these issues within the muscle? Can we see muscle changes in myositis?

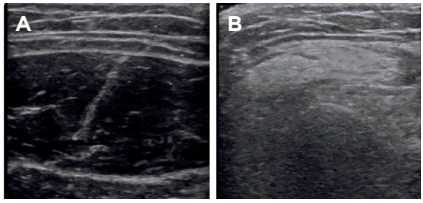
The answer was yes!

What is IBM?

IBM is one of the main forms of inflammatory myopathy. But what, exactly, is it? Is it an autoimmune process, is it degenerative – or is it both? We don't know for sure. IBM gets its name from its pathognomonic finding: *tiny inclusions*, or vacuoles, in the muscle that are visible under the microscope. It affects about 18/100,000 Americans, is three times more common in men than women, and its onset is generally over the age of 40. It affects both proximal and distal muscle groups, most prominently the quadriceps muscle and deep finger flexors leading to muscle atrophy, weakness, and significant disability. The onset of the disease is quite insidious and often missed, leading to a delay in diagnosis.

What Ultrasound Shows in IBM

Normal muscle tends to look relatively black on the screen, with whitish dots representing perimysial septa – the "starry sky" appearance. When the muscle gets affected by inflammation, it becomes a little whiter. In IBM, the muscle keeps getting damaged. It turns very white as it gets replaced by fat and fibrosis. Because it preferentially affects certain muscle groups, like the finger flexors and quadriceps, we can detect that very easily on ultrasound and compare it with adjacent unaffected muscle. It's easy to distinguish IBM from other kinds of myositis. The muscle changes in IBM are almost unequivocal, because the affected muscles get very small and white.



Rectus femoris in a normal (A) and IBM (B) patient.

Mitochondria in the Muscle

We used ultrasound – much cheaper and more accessible than MRI – in a recent clinical trial to help us estimate muscle quality and pinpoint a location for muscle biopsy. The drug we were testing was Pioglitazone, used to improve blood sugar control in type 2 diabetes. It causes mitochondrial upregulation in the muscle, and in IBM, mitochondrial abnormalities are among the most common findings seen on muscle biopsy. Also, exercise is one of the only therapies that has shown consistent benefit for IBM, and exercise increases mitochondria in the muscle. We're just trying to mimic that with a drug. There were 13 patients in the trial, and we had one clear responder, a patient who dramatically improved on the therapy. This patient felt stronger. Strength and functional testing showed that he did improve on the drug, and his muscle enzymes went down. When we stopped the drug, his CPK went up and he got weaker. His response is helping us understand more about what drives the disease. We are now studying this further with the use of metabolomics and are finding that metabolic dysregulation

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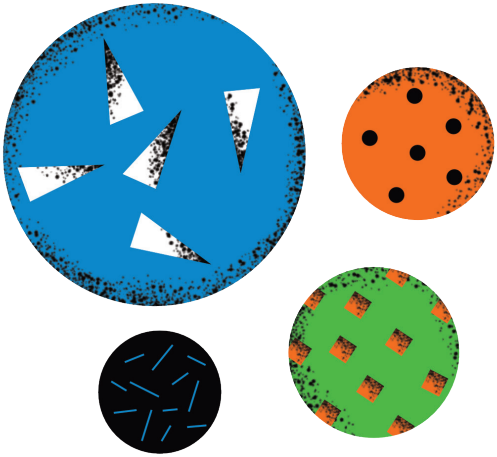

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is present in IBM and becomes more accentuated as the disease advances.

Why didn't everyone respond equally? Ultrasound sheds some light here.

Because IBM is such a chronic disease, patients tend to compensate very well, and this can be misleading. They seem to be fairly strong; they're still standing, still walking, and they get into clinical trials because they are still "high functioning". If patients can still ambulate 6 meters and get up out of a chair, that's still considered appropriate to enter a clinical trial. In our study, although some participants met all the usual criteria, when we looked with ultrasound we were very surprised to see

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Director of the Musculoskeletal Ultrasound and Injection Clinic (MUSIC) at Johns Hopkins, Associate Professor of Medicine, and Rheumatology Fellowship Program Director.

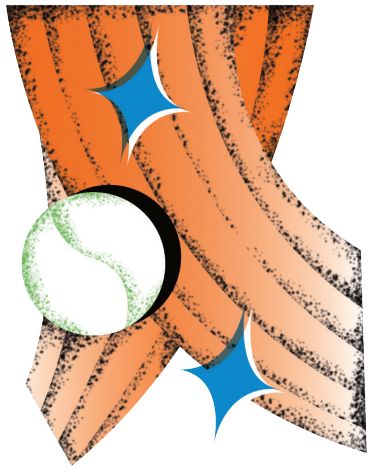
A pioneer in the use of ultrasound in rheumatology, she also heads the Rheumatology Musculoskeletal Ultrasound Program, a recognized strength of the fellowship program. Dr. Albayda has a special interest in the role of musculoskeletal ultrasound in the diagnosis, understanding, and care of all forms of arthritis and myositis, particularly IBM. She is Principal Investigator of a clinical trial of pioglitazone (Actos) in IBM. For the last two years, she has served as Chair of the Ultrasound Planning Committee of the American College of Rheumatology (ACR), and is heading a revision of ACR guidelines for musculoskeletal ultrasound use in soft tissue and procedures. She mentors other specialists in muscle ultrasound of dermatomyositis and myopathies, and is working to standardize the use of muscle ultrasound for myositis and clarify the appearance of muscle inflammation versus damage. She is part of an international Outcome Measures in Rheumatoid Arthritis Clinical Trial (OMERACT) working group for muscle ultrasound. Dr. Albayda also serves as a mentor and leads workshops for muscle ultrasound through the U.S.-based Ultrasound School of North American Rheumatologists (USSONAR).

that their disease was way more advanced than we thought. The muscle was already very dense and very white; it was pretty much replaced by fat. The human body is amazing! You wonder how people are walking independently when there's very little muscle.

Ultimately, we learned that one reason why some people didn't do well in the clinical trial was because they were already far advanced. If you don't have much muscle, nothing is going to help that. So, we're probably enrolling the wrong people, and that's possibly one reason why the trials are failing. We are now working to create a severity score based on how the muscle looks on ultrasound – so we have another parameter to assess not just muscle function, but also muscle structure, and that can add another parameter to how we define someone's entire disease.

IBM patients are a heterogeneous group, and it always helps to try to make things more homogeneous.

We can do that in several ways. We could group people by similar findings on muscle biopsy or by the presence of antibodies, for example. Or we could try to group patients by disease stage or severity (degree of fat replacement/atrophy seen on imaging)—something I've been thinking about a lot since this trial. We don't really know the pathogenesis of IBM and it may start out as more inflammatory, then it becomes degenerative; or it's a degenerative process that causes inflammation. If we were able to study people earlier in their disease, and then those later in the disease, would we find more commonalities that drive it? And perhaps one of the reasons why we don't find a clear story is that we are currently just lumping everybody together, including a lot of people with late-stage disease that acts very differently. Muscle ultrasound could be very useful here. There's a clear need in IBM, and the more we learn, the more we can find therapeutic avenues.



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Ultrasound Standards for IBM

MRI is very expensive and can be claustrophobic; we can't afford to have everyone undergo repeated MRIs especially for a clinical trial. At the Johns Hopkins Myositis Center, we are working to develop and quantify

ultrasound standards that we hope can be implemented at other institutions – to help determine, for instance, whether someone has earlier disease and could respond to a drug, or whether the disease is far advanced and the patient would not be a good candidate for a clinical trial. It can be used as part of diagnosis and also in following our patients long-term. Ultrasound is easy and inexpensive – I can even use a handheld probe attached to my phone – but it's quite subjective and requires experience. That's why our fellows here go through a rigorous training in ultrasound, to ensure that they are highly skilled in both scanning and interpreting pathology.

Final Thoughts on Ultrasound

I believe ultrasound helps us take better care of patients. I don't have to send someone for an MRI and wait two weeks. I can look right now at the bedside and show it to the patient. What other imaging modality can you be truly involved in generating as a rheumatologist? This simple, humble kind of technology has had a resurgence, and we're using it more and more, with better clarity and real-time feedback. Ultrasound has been for me a great joy!

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FURTHER READING

Diagnostic Value of Muscle Ultrasound for Myopathies and Myositis.
Curr Rheumatol Rep
2020, PMID:32989482

Ultrasound can differentiate inclusion body myositis from disease mimics.
Muscle Nerve
2020, PMID:32239702

Automated diagnosis of myositis from muscle ultrasound: Exploring the use of machine learning and deep learning methods.
PLoS One
2017, PMID:28854220

Pattern of muscle involvement in inclusion body myositis: a sonographic study.
Clin Exp Rheumatol
2018, PMID:29745890

6 TRIALS

Current clinical trials at the Johns Hopkins Myositis Center including 2 for IBM

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The publication of *LEAP Rounds* is made possible through a grant from the Jerome L. Greene Foundation

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2007

year the multidisciplinary Johns Hopkins Myositis Center opened

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