Unraveling the Mysteries of Novel, Rare Rheumatic Diseases – Part 2

Transcript

Peter Grayson, MD (Guest): Is it worthwhile to do research in rare diseases? I would say that that is, overwhelmingly, a yes!

Meghna Rao (Host): Welcome to *Rheum Advisor on Air*, the official podcast of *Rheumatology Advisor*, one of Haymarket Media's leading publications that focuses on the latest news and research in rheumatology to inform clinical practices. I'm your host, Meghna Rao, the editor of *Rheumatology Advisor*. In this podcast series, we will be looking at emerging topics in the field of rheumatology from various experts. These perspectives may be related to the diagnosis and treatment of rheumatic diseases, current guidelines, practice management, patient care, and much more.

Meghna: I remember scrolling through my Twitter feed in October last year to see a headline from the [National Institutes of Health] (NIH) that read, "Scientists use clues in the human genome to discover new inflammatory syndrome." Ever since then, I've been waiting to talk to my next guest, who of course, is no stranger to the limelight for his incredible contributions to rheumatology research. Dr Peter Grayson, the head of the Vasculitis Translational Research Program at the National Institute of Arthritis and Musculoskeletal and Skin Diseases. He's also on the board of directors of the Vasculitis Foundation and a steering committee member of the Vasculitis Clinical Research Consortium.

I don't think I did your introduction very much justice, but Dr Grayson, thank you so much for joining me today to shed light on a very important aspect of rheumatic disease research that can potentially inform better therapeutic options and outcomes in time. Now, in the first part of this series, I had a similar dialogue about rare rheumatic disease research and its effect on patients that I hope to continue in this episode.

Dr Grayson: Thank you so much for having me. It's a pleasure to be here.

Meghna: Let's start our conversation today by addressing what was a super exciting research revelation for you and your team – the discovery of the autoinflammatory disease that is being called the VEXAS syndrome. Tell us, Dr Grayson, what led to the discovery of this disease, or rather, the cause of this disease.

Dr Grayson: Yeah, the VEXAS story just came out at the end of last year. It's a really amazing story that I think speaks to the best parts of the National Institutes of Health because it was discovered by a large group of physician scientists working together within the Intramural Research Program at the NIH to solve a medical mystery. One of the aspects is that there is a

program there called The Undiagnosed Diseases Program, where physicians from around the country can refer patients who have atypical symptoms and for whom they just can't quite make a diagnosis.

We had seen a couple of patients within that program who had a strange constellation of symptoms that included really severe inflammation that was refractory to treatment, along with progressive bone marrow failure. This [crossroad] of rheumatologic problems with hematologic problems was quite strange to us.

In the summer of 2019, I got a phone call from a clinical geneticist named David Beck, who's working in Dan Kastner's group at the NIH, and he had done something quite radical. He had taken existing databases of DNA sequencing data from The Undiagnosed Diseases Program and from Dr Kastner's group and had explored it for mutations in the ubiquitin pathway, without paying any attention to the clinical symptoms of patients that were in that database. He found 3 men who had these mutations in a gene called *UBA1*. When he went and looked back at the charts of those men, they were these patients that we had originally seen in The Undiagnosed Diseases Programs, with these strange hematologic and rheumatologic problems.

Meghna: Yeah, it is fascinating, right, to find these answers, and in this case, finding the specific mutation itself that may be responsible for causing the inflammatory condition. And the fact that patients may not have inherited it, but they developed it later in life. It must have been a challenge because all these patients who you described in the study and who visited the NIH [had] seemingly unrelated but overlapping clinical manifestations.

Dr Grayson: Well, when the good Dr Beck saw this mutation and came to me and we started talking about these patients, we first thought that this was a disease that was restricted to certain clinical features. But it kicked off this long discovery process where a lot of different groups were involved where we started to realize that this disease, which we have named the VEXAS syndrome, the inflammation in it can look like a lot of different diseases. And, every patient with the VEXAS syndrome is an older man, because it's an X-linked gene, so it functions as an X-linked recessive disease. They had various forms of vasculitis and chondritis, including relapsing polychondritis.

It was just serendipitous, I think, for our team to be involved in this story because we have spent the last 5 to 7 years working at the NIH, clinically studying rare forms of vasculitis, and we launched a relapsing polychondritis program, so we've been studying chondritis. It's mind blowing to me that this new disease combines elements of both vasculitis and chondritis. So, within our own cohort at the NIH, we started to discover a lot of patients that had this mutation, that have the VEXAS syndrome, because it's enriched for that type of phenotype that we had been studying.

The other thing that you pointed out is that this was a somatic mutation; it's not inherited. That made it a little more, even more challenging, because these patients had acquired this mutation in their bone marrow. So, they didn't inherit it from their parents. That's why we

think it starts late in life. We think that this could really break open a new line of thinking in rheumatology.

A lot of these inflammation diseases that start when you're in your 50s, 60s, and 70s, and beyond, if there is a genetic driver of those, it seems less likely that that's going to be what's called a germline mutation, or a mutation that's inherited. But the idea that it could be an acquired mutation, just like what we see with cancer, really makes a lot of sense for rheumatologic diseases.

Meghna: That's fascinating! I think this discovery also underlies something larger, which is that somatic mutation, like you mentioned, may be a more common aspect of human disease than was previously thought, which, [a]gain, opens up a different perspective on the diagnosis and screening for autoimmune, inflammatory rheumatic diseases, overall.

Dr Grayson: Yeah, that's true. I mean, to detect a somatic mutation in DNA, there are certain ways that you analyze the DNA that are a little bit different than the traditional ways. And, [a] part of David Beck's really keen insight into this process was that he considered somatic mutations in *[inaudible].* Because this an X-linked gene, what he was seeing was multiple allele reads, 2 allele reads in the men when they should only have 1.

Many people would have assumed that that was sequencing artifactory error. But we pursued it. It opens up this idea that when we're doing DNA analyses, we need to be, perhaps, a little more open minded in the types of inheritance and the patterns of inheritance that we're looking for.

Meghna: Yeah, and also, to add a mental note here about addressing the risk for missed diagnoses, or in this case, maybe the underdiagnosis of rare and new diseases.

Dr Grayson: Yeah, it's a fascinating thing because when we saw these patients, they were diagnosed with conditions like polyarteritis nodosa, giant cell arteritis, [Sweet] syndrome, [and] relapsing polychondritis. Those, we think, were accurate diagnoses; [patients] actually had the clinical features of those diseases; they had biopsy proof of those conditions. So it's not like they were being misdiagnosed. But what the VEXAS syndrome does is it actually provides a molecular diagnosis or a genetic diagnosis that complements our clinical assessment.

I think that that's really one of the things that's impressive about this disease is that, in rheumatology, we see these very complicated diseases that we think are likely due to complex factors and that it's very hard to unravel. But VEXAS is proof that you have a very complex phenotype that's due to a monogenic driver. So, in a sense, we can boil down complex diseases to their essential elements, and I think we should be striving to do that across that board in rheumatologic conditions.

Meghna: You're absolutely right, and [this is] a great segue to my next question. [I] had a chance to read and listen to several of your interviews where you've always maintained that rheumatic diseases are some of the most complex conditions, with diagnosis being challenging

due to the varying nature of the symptoms. Now, in terms of VEXAS, you and your team were [a]ble to get right down to the molecular level using a genotype first approach. But could you speak to the overall importance, Dr Grayson, of clinical and translational research to better understand novel, and perhaps, rare diseases such as VEXAS?

Dr Grayson: Yeah, I think what's fundamentally inherent to that question is – is it worthwhile to do research in rare diseases? I would say that that is, overwhelmingly, a yes! It's worthwhile for a number of reasons. One is that rare diseases have a lot to teach us and the implications of what we can learn in rare diseases are often much broader than that disease itself. For example, there are genetic diseases where you have a defect in [a] specific part of the immune system. The opportunity to learn what that part of the immune system does and how it functions when it's perturbed is really profound, and it's taught us a lot of human immunology.

The other reason why I think it's super important to do rare disease research is because, as many people say, and my former mentor, [Dr] Peter Merkel would [always] say to me, "It's a rare disease unless you have it; then it's not rare anymore and it's a common experience for you that you deal with every day." I believe strongly that the benefits of research should be just for everybody. Patients with rare disease face a ton of challenges that are shared amongst all of these kinds of patients. There's long diagnostic delays. The medical community isn't necessarily as trained to recognize their super rare condition. It's hard to do clinical trials to figure out if drugs work or not because it's hard to recruit the number of patients, and the diseases can be quite debilitating and [v]ery isolating on the patient level. So I think that, for me, the great honor of my job and career is to be able to partner with these extraordinary patients to try to use research to improve their lives in real time.

Meghna: That's amazing! Just to add to what you said, I think this kind of research also paves the way for better classification of inflammatory diseases in general.

Dr Grayson: Yeah, I would love to — I've spent a long time, since I was a rheumatology fellow, thinking about disease classification. If you look at the evolution of it, we classify our diseases based on the pattern of clinical symptoms. It's a pretty crude thing. We do the best we can. We recognize that a lot of our conditions overlap with each other quite a bit. I think that we can do better.

What would ultimately do better is biologic classification of disease, incorporating molecular data with clinical data and trying to come up with schema that enable us to have precision medicine approaches. I am always impressed by how cancer research tends to lead the way. In the modern era, it's inconceivable not to clinical genomics as part of cancer treatment. I'm excited to see those kinds of techniques get further incorporated into clinical rheumatology.

Meghna: On that note, what specific tools were used to study VEXAS, and what do you think can be useful to advance rheumatic disease research at a genetic or molecular level in the future?

Dr Grayson: One of the things that enabled the discovery of VEXAS is the accumulation of whole-exome sequencing database level data in patients that had good clinical phenotyping as well. It is very discouraging on one level that patients that come through The Undiagnosed Diseases Program, for example, it's only the minority of them in which they can arrive at a diagnosis or a new disease discovery, this kind of thing. But as these databases accumulate, there's value there.

The ability to start looking in a genotype-first way at all of this accumulated genetic data may really enable us to discover diseases that are much more challenging to recognize at the bedside. So I really am a big believer that we should be genotyping patients across the board, and getting consent to do this, and getting genetic data, and using [those] data in a publicly available way to start to try to unravel these diseases more at a molecular level.

Meghna: Just looking at the bigger picture, I think data registries, especially rheumatology-specific ones like the ACR's Rise Registry, can play an integral role in providing robust information about patients with rheumatic diseases.

Dr Grayson: I totally agree. The thing that is, [t]o me, [s]eems so crude right now, which I wish we could get better at, is that how it works is, you see a patient with once-in-a-lifetime constellation of symptoms. You think about that patient and that case stays with you. Maybe you talk about that patient informally with colleagues. At some point, maybe you find another physician that has seen the exact same thing. If you find more than 1 of the same type of rare phenotype, then you've got something to really work on and you can make some discovery.

It really is fascinating to me that we haven't done a better job of organizing that on a national level. It would be really nice if we were able to sort of communicate to each other faster in real time to share these once in a lifetime cases and to find patients with phenotypes that overlap. Because if we had that source of dialogue, I think it would really accelerate disease discovery. Once we defined the phenotype of VEXAS, for example, and put it out there to the world, then physicians find these patients; they have them. We actually think that this disease isn't as rare as people suspect; it just needed to be defined. Once it's well defined, you start to be able to recognize it. But if we had been having open communication and sharing these weird phenotypes, I think it would accelerate that process.

Meghna: I just wanted to also ask you, what's next for VEXAS? Is there research in the pipeline, possibly towards developing therapeutic options? I'm thinking maybe genome-editing here.

Dr Grayson: Yeah, next is treatment for us, that's our big concern, because the disease is quite serious for many of the patients. There's a high mortality rate. We have yet to identify any therapy that has convincing efficacy beyond glucocorticoids, which come with a whole host of problems. So we definitely want to find therapies that are helpful to this patient population, whether that's medical therapy or more aggressive procedures like bone marrow transplantation. We've heard of allogenic bone marrow transplantation that's happened in at

least 2 patients with the VEXAS syndrome who did well. That potentially could be a curative therapy.

A gene editing approach is, as you mentioned, would be ideal in this kind of disease. It's a long road to go. The problem with VEXAS, as well, is that it's an older population. So there's potential comorbidities and things that would make them less than ideal transplant candidates. So in parallel with things like bone marrow transplantation, we're still looking very hard to try to understand the inflammatory process of the disease so that we can discover and develop therapies for the condition. That's 1 aspect of what's next for VEXAS.

I think what's next for VEXAS, beyond just our group and the NIH investigators that work on it, is you're going to start to see more and more of these cases being identified around the world and different cohorts reporting on them. We're already hearing about colleagues in Europe and Asia that are discovering a lot of these patients. I think what also is next for VEXAS is that this is a disease that's an overlap between hematology and rheumatology. So it really provides a nice framework for us to start to collaborate and work more closely, as rheumatologists, with our hematology colleagues. We're also seeing this in — with checkpoint inhibitor induced autoimmunity.

I believe that VEXAS is a prototype for a new class of disease, defined by mutation in bone marrow stem cells that lead to inflammation. I think we will find other disease beyond VEXAS, where other genes are potentially at play.

Meghna: Wow, an exciting endeavor, for sure! This has been a wonderful conversation, Dr Grayson. Thank you so much for taking the time, and I hope to continue to see your work on my Twitter feed.

Dr Grayson: Thank you for having me. I hope to continue to provide that work into your Twitter feed.

Meghna: Please stay tuned for more episodes in this series. For more information on *Rheumatology Advisor* and this podcast, you can reach out to us at editor@rheumatologyadvisor.com. We, at *Rheumatology Advisor*, look forward to delivering timely, evidence-based news to you. You can also sign up for our free newsletters on the site.