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Unraveling PMR Pathophysiology: The Central Role of IL-6

Announcer:
You're listening to ReachMD. This medical industry feature, "Unraveling PMR Pathophysiology: The Central Role of IL-6," is brought to you by Sanofi and Regeneron. Here's your host, Dr Charles Turck.

Dr Turck:
This is ReachMD, and I'm Dr Charles Turck.

Today, we'll be reviewing the pathophysiology of polymyalgia rheumatica, or PMR, and how IL-6 plays a role in it. Joining us for this discussion are Dr Adam Brown, an expert from the Cleveland Clinic, and Dr Megan Sullivan, an expert from the Mayo Clinic.

Dr Brown, Dr Sullivan, welcome to you both!

Dr Brown:
Thank you for having me.

Dr Sullivan:
Happy to be here.

Dr Turck:
Starting with you, Dr Brown, would you give us an overview of PMR and how it typically presents?

Dr Brown:
Of course. Simply put, PMR is an inflammatory disease, and we generally see it affecting individuals who are older than 50 years of age.[1,2]

When it comes to symptoms, PMR is characterized by pain and stiffness. You'll usually see that manifesting in the shoulders, neck, and hips, and it often leads to significant disability and an impaired quality of life. In its classic form, PMR often presents quite dramatically, with severe and symmetric pain that emanates from the periarticular structures of the shoulders and hips.[1,2]

Dr Turck:
But it's not always that "classic" presentation, is that right?

Dr Brown:
That's exactly right. PMR can present atypically, so you might see features such as neck pain, unilateral shoulder pain, or even lower leg pain. It can also involve carpal tunnel syndrome and tenosynovitis in the hands and/or wrists. And so all of these various manifestations make it quite challenging to diagnose.[2]

Dr Turck:
Let's turn to you now, Dr Sullivan. How common is PMR?

Dr Sullivan:
PMR is actually the second most common rheumatic disease in adults older than 50 years of age—second only to rheumatoid arthritis, or RA. While RA is the most well-known autoimmune condition affecting the joints, patients presenting after age 50 are more likely to have PMR than RA.[3,4]

Looking at the data, the annual incidence of PMR in the United States is about 64 per 100,000 people aged 50 and older. That's around

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2%, or 1 in 50 individuals, who will develop PMR. In terms of total burden, the estimated prevalence in the US is approximately 750,000 patients.[5–7]

Now, it's important to note that PMR is extremely rare among individuals younger than 50 years of age. The occurrence of PMR becomes progressively more prevalent with each passing decade, with the highest incidence peaking at approximately 75 years of age.[6,7]

Dr Turck:
That's a significant age differential. Do we know why that is?

Dr Sullivan:
Well, the precise causes aren't fully understood yet, but it's widely believed that immunosenescence—which is essentially the natural process of the immune system aging—plays a crucial role in the development of PMR.[6,7]

Dr Turck:
Now, we just discussed age as a primary driver, but, Dr Brown, what are some of the other risk factors associated with PMR?

Dr Brown:
Right, so in addition to older age, we suspect that genetic predisposition plays a role here, and we see evidence for this in its unequal geographic distribution.[8]

For instance, the incidence of PMR in northern Europe and other areas with Scandinavian populations is substantial, while in African and Native American populations, it's almost nonexistent.[8]

Dr Turck:
So there's a genetic or ancestral link here?

Dr Brown:
It seems so, especially since certain genetic variations in immune-related genes have been associated with increased susceptibility to PMR.[8,9]

We've also seen that greater disease severity and higher relapse rates may be linked to populations carrying the HLA-DRB1*04 allele. In fact, some of these HLA-DRB1 subtypes have been identified as predisposing factors for vascular complications in patients with PMR.[8,9]

Dr Turck:
Interesting. Anything else you'd like to add, Dr Sullivan?

Dr Sullivan:
Yes, I think it's important to mention immune checkpoint inhibitors. These have become increasingly common as a cancer therapy, but we're seeing that their use can be associated with an approximately 5-fold elevated risk of developing what we call a "PMR-like" illness. What's interesting is that this elevated risk hasn't been seen with other types of immunotherapies used in patients with cancer.[7,10]

Dr Turck:
Wow, a 5-fold risk is certainly concerning. So, Dr Sullivan, how closely does that "PMR-like" illness in patients with checkpoint inhibitors mimic the idiopathic version?

Dr Sullivan:
That's the big question a lot of us are asking. Researchers analyzed case reports from 3 centers in the United States and Europe and conducted a systematic review. In total, they identified 49 patients who developed a "PMR-like" illness while receiving an immune checkpoint inhibitor. The researchers wanted to see if these patients fulfilled the 2012 EULAR/ACR provisional criteria for PMR.[10]

And as it turns out, 75% of those patients did meet the criteria for a PMR classification.[10]

Dr Turck:
So for three-quarters of patients, the clinical picture is virtually identical between PMR and the "PMR-like" illness patients with immune checkpoint inhibitors experience?

Dr Sullivan:
Exactly. However, because we still don't have a "gold standard" for the diagnosis of PMR, the exact relationship between checkpoint inhibitor-related PMR and the idiopathic form remains a bit unclear. So it's definitely an area that requires more research.[10]

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Dr Turck:
Thank you both. That helps clarify the landscape of who's most at risk for PMR.

Now switching gears, lets discuss how the disease shows up in the clinic. Research suggests that PMR and giant cell arteritis, or GCA, are very closely related. Dr Brown, what do we currently know about this connection?

Dr Brown:
This is such an important point because they really are 2 sides of the same coin. We see that about 15% to 20% of PMR cases present with obvious signs of GCA, but it's even more striking in the other direction, as 40% to 60% of patients with GCA also present with PMR.[11,12]

When you look at them side-by-side, the similarities are hard to ignore. Both show significant musculoskeletal and arterial inflammation, a dominant IL-6 profile, and—typically—a very positive initial response to corticosteroids. Because they share so many epidemiological features and overlapping pathophysiology, many of us now view PMR and GCA as manifestations of the same inflammatory disease existing on a single spectrum.[12]

Dr Turck:
Another rheumatic disease that can have overlapping presentation with PMR is RA. Would you tell us more about that, Dr Brown?

Dr Brown:
Yes, so just like with GCA, distinguishing between PMR and RA can be difficult because these conditions have similar clinical presentations, such as acute involvement of the girdles, severe morning stiffness, raised ESR, and a good response to low doses of prednisone.[13]

To further complicate things, anywhere between 5% and 20% of patients with PMR will develop RA within 1 year. However, it's important to note that the exact overlap between PMR and RA is still unclear.[13,14]

Dr Turck:
With all that in mind, let's dive into the pathophysiology of PMR. Dr Sullivan, what's happening under the hood when the immune response is activated in PMR?

Dr Sullivan:
Well, broadly speaking, it's an aberrant activation of both the innate and adaptive branches of the immune system. This immune response leads to the secretion of several pro-inflammatory cytokines, things like TNFα, IL-1, IL-10, IL-17, IFNγ, and, of course, IL-6.[15]

We think IL-6 is really the "engine" here. Unlike most cytokines, which have natural mechanisms to limit their activity, IL-6 can amplify its own production, creating a self-sustaining cycle of inflammation.[16]

It's been shown to play a role in other chronic rheumatic diseases like RA, and it drives the systemic inflammation that we see in PMR.[17] Additionally, IL-6 is directly responsible for inducing the acute-phase reactants we use as markers of disease activity, like C-reactive protein and erythrocyte sedimentation rate, or CRP and ESR, respectively.[15]

Dr Turck:
And is this process systemic or local, Dr Brown?

Dr Brown:
It's a bit of both. The primary "ground zero" involves the periarticular structures around the shoulders and hips—specifically, the extrasynovial and interspinous bursae.[18]

What's interesting, though, is that the immune signature in the synovium can be quite different from what we see in the peripheral blood. In the blood, we see an increase in the proinflammatory Th17 cells and a drop in immunosuppressive Treg cells. But in the synovium, it's mostly macrophages and CD4+ memory cells. We actually don't see B cells or NK cells there at all. This suggests that the localized inflammation within the synovium creates its own unique molecular "micro-environment", which contributes to the pain and stiffness patients experience.[12,15,19]

Dr Turck:
Thank you for that explanation, Dr Brown. And coming back to you, Dr. Sullivan, would you expand on some of the changes that are seen in the peripheral blood?

Dr Sullivan:
Yes, in the peripheral blood, there are detectable changes in the immune system, including an increase in certain innate and adaptive

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immune cells, circulating cytokines, and elevated levels of acute-phase reactants like CRP and ESR; these indicate ongoing systemic inflammation. This systemic inflammation likely contributes to symptoms such as fatigue, malaise, anorexia, weight loss, and low-grade fever, which are experienced by approximately half of patients with PMR.[20]

Dr Turck:
And what about in the synovium?

Dr Sullivan:
In the synovium, macrophages, along with T cells, infiltrate synovial tissues and temporal arteries of patients with PMR, leading to localized inflammation and the hallmark symptoms of pain and stiffness in the affected areas.[15,21]

Dr Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and I'm speaking with Dr Adam Brown and Dr Megan Sullivan about the pathophysiology of polymyalgia rheumatica, or PMR.

Let's now focus in on IL-6. Dr Brown, would you elaborate on its role in the PMR pathophysiology?

Dr Brown:
Of course. As Dr Sullivan alluded to earlier, IL-6 is believed to be a major driver of PMR pathogenesis since IL-6 levels correlate with disease activity.[20]

In one study, while healthy controls had minimal detectable plasma levels of IL-6, patients with PMR were characterized by significantly increased concentrations of plasma IL-6 before treatment was initiated.[22]

Additionally, other studies have shown that IL-6 levels are rapidly suppressed by corticosteroids. However, plasma IL-6 levels immediately increase upon short-term discontinuation of corticosteroids, despite several months of treatment, suggesting that corticosteroids do not correct the underlying mechanism that causes elevated IL-6 levels in PMR.[23]

In the last study I'd like to highlight, the IL-6 promoter genotype was assessed in both control patients and patients with PMR to determine whether the polymorphism modulated circulating IL-6 levels and influenced PMR severity. The study found that, regardless of genotype, elevated IL-6 levels were associated with relapse and recurrence.[24]

Dr Turck:
Those are some interesting findings, Dr Brown. Dr Sullivan, what else do we currently know about the role of IL-6 in PMR?

Dr Sullivan:
Since soluble IL-6 receptor levels correlate with the number of relapses, IL-6 has been suggested to serve as prognostic markers of PMR outcomes. In fact, when patients were divided according to outcome—meaning no relapses, 1 relapse, or at least 2 relapses—significant differences in soluble IL-6 receptor levels were observed, with the highest concentration corresponding to the group of patients who have experienced at least 2 relapses. Therefore, circulating levels of soluble IL-6 receptor may predict future relapses in patients with PMR.[25]

So to summarize, IL-6 plays a central role in the pathogenesis of PMR because high IL-6 and soluble IL-6 receptor levels are associated with disease activity, increased risk of relapse, and recurrence of PMR symptoms.[22,24,25]

Dr Turck:
If we keep digging into this, Dr Brown, would you expand on how differences in levels of IL-6 impact PMR pathophysiology?

Dr Brown:
Sure. IL-6 can exert its effects in multiple tissues to affect both systemic and local inflammation.[7,9,26]

If we look at systemic inflammation first, patients with PMR had increased levels of IL-6 in the plasma and the serum. One study found the presence of IL-6 in the serum correlated with CRP and ESR.[7]

And when it comes to local inflammation, IL-6 is expressed in the synovial tissue of patients with new-onset, treatment-naïve PMR, where it is thought to drive local inflammation.[9,26]

My final point is that within the synovial tissue, IL-6 is widely expressed by various cell populations in the subacromial-subdeltoid bursa of patients with PMR, such as CD34+ endothelial cells, CD34+ fibroblasts and stromal cells, CD90+ fibroblasts, and CD68+ macrophages.[26]

Dr Turck:

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Well, it's clear that we keep coming back to IL-6 as the major driver of PMR. So, Dr Sullivan, why does it have such an impact compared to other cytokines?

Dr Sullivan:
It's because of its unique dual-signaling mechanism.

Let's look at cis-signaling first. This uses membrane-bound IL-6 receptors found on a limited set of cells, like hepatocytes and certain leukocytes, and it's usually involved in homeostatic or protective functions.[27,28]

Trans-signaling, on the otherside, is the one we care about in inflammatory disease. It uses soluble IL-6 receptor to engage a much wider range of cells that don't even have membrane receptors, like osteoclasts, fibroblasts, and even neural cells.[27,29]

For either of those to work, you need signal-transducing glycoprotein 130. Once that complex docks, it triggers the JAK/STAT, MAP-kinase, and PI3kinase pathways, which drive inflammatory processes. That's why IL-6 can influence so many different organs and tissues at once.[28]

Dr Turck:
With that in mind, Dr Brown, how do these microscopic pathways translate to the actual symptoms like fatigue, pain, and morning stiffness?

Dr Brown:
It's surprisingly direct. IL-6 stimulates the hypothalamic-pituitary-adrenal, or HPA, axis, which is where the fatigue and mood disturbances come from.[21,30]

We've also found that IL-6 follows a circadian rhythm. It peaks in the early hours of the morning, which correlates perfectly with the timing of classic morning stiffness. When we treat PMR patients with glucocorticoids, we see a marked reduction in both the IL-6 levels and the duration of that stiffness.[31]

Now, when it comes to the pain cycle, IL-6 amplifies pain perception in both the central nervous system and the periphery.[32] Pain disrupts sleep, and that lack of sleep lowers the pain threshold further. It becomes a vicious cycle of chronic pain, fatigue, and mood issues that define the PMR experience.[33]

Dr Turck:
Well, we're almost out of time for today, but before we close, I'd like to ask each of you one more question. Dr Sullivan, any final thoughts on why age plays such a large role in PMR?

Dr Sullivan:
Well, as we age, our tissues lose elasticity and become more vulnerable to microdamage, which releases "danger signals" that activate the immune system. Combine that with an aging immune system that already has higher baseline IL-6 levels, and you have the perfect storm for PMR.[34,35]

Dr Turck:
Thanks, Dr Sullivan. And let's turn to you, Dr Brown, for the final word. Given everything we discussed today, where do we go from here?

Dr Brown:
Well, we've known about PMR since the 1940s[36], and with biologics, we are now learning more about how to manage this disease.

Currently, PMR disease activity is monitored primarily through symptoms and clinical assessments. However, having reliable biological markers could make it easier to track disease activity and better predict how the disease will progress. IL-6 has been shown to correlate with disease activity and relapse and therefore has been suggested as a potential marker for PMR. Identifying biomarkers that are linked to disease activity may help support earlier diagnosis, provide insight into treatment response, and identify patients at greater risk of relapse.

Dr Turck:
Those are great closing comments, and I want to thank my guests, Dr Adam Brown and Dr Megan Sullivan, for sharing their insights on the pathophysiology of PMR. Dr Brown, Dr Sullivan, it was great speaking with you both today!

Dr Brown:
Thank you.

Dr Sullivan:

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It was a pleasure.

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MAT-US-2609338-V1.0 – 09/2026