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Pulmonary Hypertension in a Patient With Adult-Onset Still's Disease

Dr. Saggar:
Hello, I'm Dr. Rajan Saggar. And I'm here to discuss a very interesting case with you about pulmonary hypertension in a patient with Adult-Onset Still's Disease. The patient is a 38-year-old female who is diagnosed with Adult-Onset Still's Disease in April of 2020. And at that point, this patient met the Yamaguchi criteria and presented with prolonged fever, high-grade fever of 103 to 104 degrees Fahrenheit for over one month, profound myalgias and arthralgias, involving the upper, greater than lower extremities, nausea, vomiting, and stool frequency, as well as a nonpruritic rash involving her forearms and legs, more so than her face and torso. And, finally, splenomegaly, mildly abnormal liver function tests in terms of a transaminitis, and the patient was negative for ANA and rheumatoid factor.

So if you look at this next slide, you can see the course of therapy for this patient with Still's disease. Again, the diagnosis was April of 2020, and we met the patient in November of 2021. And you can see that she had several therapies on board, including etanercept in May of 2020. And then in place of etanercept was the IL-6 inhibitor, sarilumab, and then in December of 2020, sarilumab was stopped and converted to the IL-1 receptor antagonist, anakinra. And after that, interestingly enough, the patient was placed on methotrexate in addition to corticosteroids and anakinra and was doing quite well if you look at the ferritin values below at which time she actually had a value of 200 nanograms per milliliter. And unfortunately, after getting the COVID vaccine, it is clear that, and according to the patient as well, that she had a worsening of her underlying symptomatology related to Still's disease and reflected in increasing ferritin values. So in November 2021, when we met the patient, she presented with progressive dyspnea on exertion and a non-productive cough, spanning approximately eight weeks, which was unresponsive to at least two rounds of outpatient antibiotics. Her ferritin had increased to just above 5,500, she had an intermittent fever, relative tachycardia, and a slight recurrence of the rash on her forearms, and in initial pulse oxymetry, relatively reduced at 90% on room air. Her vital signs are as listed. The echocardiogram showed a small left ventricle of flattened intraventricular septum during systole and evidence for right-sided chamber enlargement and evidence for pulmonary hypertension.

The patient's right heart catheter data are noted on the left. In November 17th, 2021, the patient had a mean pulmonary pressure of 47 millimeters of mercury and a cardiac index of 2.45 liters per meter squared and no response to inhaled nitric oxide with a normal filling pressure in terms of a right atrial pressure. The labs were interesting. And on the right, you can see the patient had a relative anemia and leukopenia, as well as a mild transaminitis, mostly in the form of AST and the elevated ferritin above 5,500 and a C-reactive protein, which was 52.95, highly elevated with otherwise normal renal function and no signs of an infectious process per say.

So, in the next slide here, you can see the three time points, November 18th, 2021 and the associated lab values, including ferritin and C-reactive protein, which are commonly tracked in Still's disease as a measure of inflammatory activity and the pulmonary hypertension-related labs including brain natriuretic peptide and the troponin I at these three different time points.

And what you can see here are the chest x-rays on the left, and in the middle, the CT scan of the chest, and on the right, the echocardiograms. And the point of all this is to show that the clinical activity of the pulmonary embarrassment was well-associated and correlated with the decreasing ferritin and C-reactive protein. And you can see this by imaging as well as near normalization of the right heart function on the echocardiogram as well on the panel on the right in the lower-most time point, January 7th, 2022.

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So to go over the clinical course of this patient, you can see that when the patient presented to us, she was on anakinra, corticosteroids, and methotrexate and that was stopped and replaced with cyclosporine and a dose of Rituxan was given. There was a concern in early December for macrophage-activating syndrome, which commonly can be a difficult thing to distinguish between that, as well as active Adult-Onset Still's Disease. So the patient was started on etoposide and dexamethasone for MAS and the cyclosporine was stopped and the anakinra was changed from BID to QID dosing. The patient then went on to get at least two doses of tocilizumab, but remained and received at least four doses of etoposide and decreasing doses of dexamethasone. Eventually, the patient was started on ruxolitinib in December 29th, 2021, which is a JAK inhibitor. In January 6th, 2021, with clear improvement, the anakinra was decreased to BID dosing and the dexamethasone was weaned and the patient remained on ruxolitinib. The pulmonary hypertension regimen is right below there. She was immediately started when she was transferred to us on tadalafil and macitentan, and that was continued through the entire course of the patient's hospital course. You can see the ferritin values track very nicely. The patient had a peak ferritin, over 115,000, and that decreased nicely to just above 7,000. And I also put there the natural killer cell cytotoxicity assay results, the lumbar puncture results, and the IL-2 soluble receptor results.

So, by way of discussion, Adult-Onset Still's Disease is a rare disease with an incidence of 1.6 cases per million. It can be classified as either monophasic, intermittent, or chronic, and it can be complicated by macrophage-activating syndrome in approximately 1.7% of cases. It can also be complicated, importantly, by interstitial pneumonia, pleural effusion, and/or transient pulmonary infiltrates. Looking through the literature, there are approximately 22 cases only describing PAH associated with Adult-Onset Still's Disease. And there appears to be an association with severe, persistent Still's disease and a reported 22% mortality.

So the concept of pulmonary artery inflammation or vasculitis is something that really began with lupus and its association with PAH, which was first described, really, here in the New England Journal in the early 1970s. And if you go on and you look at an article from 1982, we can see here that this report is a patient who had systemic or systemic lupus erythematosus or SLE that was responsive to corticosteroids. And you can see the heart catheterization before and after steroids showing improvement, but not normalization of pulmonary hemodynamics. And, in fact, in the pathology of this patient on histology, it was noted that the pulmonary vasculature in SLE suggested that there is an early inflammatory stage which is expressed as vasculitis. And this has been an age old controversy in terms of whether something can be reversed with anti-inflammatory therapy in the setting of PAH.

In general, connective tissue disease and associated PAH are more likely to receive immunosuppression than idiopathic PAH. This data here on the left is from the REVEAL Registry, showing that patients with connective tissue disease actually receive more immunosuppression than their counterparts with idiopathic pulmonary arterial hypertension. And then moving to the right here, you can see that patients who have lupus, compared to systemic sclerosis, receive more immunosuppression as well despite the fact that they're both exposed to the same amount of combination PAH therapy. And on the right here, the point here is that lupus patients tend to do much better in terms of their PAH in terms of mortality over time compared to their counterpart, systemic sclerosis, again suggesting the concept of potential immunosuppression being or working in patients with SLE compared to systemic sclerosis.

So the response to immunosuppression is really described nicely by the French groups that looked at a study where they actually looked at patients who responded and did not respond to first line immunosuppressive therapy in the setting of SLE. And you can see here that these patients had severe pulmonary arterial hypertension and this is the response, hemodynamically, to immunosuppression only. This is without PAH-specific therapy. And they proposed an algorithm that you can see here on the right to follow these patients. And the idea being that some of these patients with SLE and PAH are treatable with immunosuppression alone, but some patients may require immunosuppression and PAH-specific therapy. Some of that is dictated by New York Heart Association Functional Class as well as their opening cardiac index on right heart catheterization.

The concept of PAH and inflammation is not foreign. And, in fact, the articles looking at the modern pathology of pulmonary arterial hypertension which was published in the Blue Journal in 2012 show that in patients with advanced PAH, this is group one PAH, there is a distinct spectrum of pulmonary vascular and nonvascular pathologies, including localized, interstitial, and perivascular inflammation. And, in fact, more recently, there was a multicenter, double-blind, randomized, placebo-control trial looking at the use of rituximab in the treatment of patients with systemic sclerosis-associated PAH. So, again, inflammation in PAH is not only something that's been recognized but has recently been targeted with rituximab.

In conclusion, Adult-Onset Still's Disease may be associated with PAH. And this PAH may respond to immunosuppression with or without PAH-specific therapy, similar to what has been noted over the last several decades with lupus. And in this patient, one of the things we are going to look onto in the future is whether the PAH therapy can actually be withdrawn in this patient as the patient remains on two oral PAH-specific therapies. That's the end of my presentation. Thank you very much.

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