Adalimumab as a potential treatment for postural orthostatic tachycardia syndrome

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Introduction

Postural orthostatic tachycardia syndrome (POTS) is a condition that affects circulation (blood flow). The diagnostic criteria for POTS are well described. POTS can be clinically defined by lightheadedness, palpitations, tachycardia, exercise intolerance, or generalized fatigue that occurs with a rise from a recumbent position, leading to an increase in heart rate of 30 beats/min (40 beats/min for ages 12–19) or more for more than 30 seconds in the absence of a drop in systolic blood pressure over 20 mm Hg.1 The disease’s epidemiology is also well documented, as multiple independent studies suggest the prevalence of POTS to be around 0.2%, with 75% of patients being female. In contrast, the physiology of POTS is not as agreed upon and can vary greatly from case to case. Several mechanisms have been proposed, many of which contain considerable overlap and can occur concomitantly in the same patient. There is evidence suggesting that hypovolemia may play a role, as up to 70% of POTS patients have a reduced blood volume.2 Fifty percent of patients present with hyperadrenergic symptoms, with increases in systolic blood pressure and plasma norepinephrine levels upon rising from recumbency. A growing body of evidence has shown that POTS may have an autoimmune basis. Multiple studies have shown various autoantibodies in conditions leading to dysautonomia.3,4 Therefore, it was hypothesized that autoantibodies against adrenergic and muscarinic receptors may play a prominent role in the pathophysiology of POTS.5 Here, we present a young female patient with a medical history significant for seronegative ankylosing spondylitis (SAS) and POTS. In a manner previously undescribed, our patient had complete resolution of POTS-related symptoms with adalimumab prescribed for her SAS. This case is of great importance because it continues to reaffirm the notion of POTS as an autoimmune disease and illustrates the potential for a paradigm shift in how we view and treat patients with POTS moving forward.

Case report

A 29-year-old female patient with a past medical history of Ehlers-Danlos syndrome, mast cell activation syndrome, SAS, and POTS was seen in the outpatient clinic for POTS. She was recently started on adalimumab for her SAS. Her POTS symptoms began in high school, as she reported feelings of lightheadedness, fatigue, palpitations, dizziness but was subsequently discharged with suspected anxiety. She also purchased a glucometer because she noticed that some of her symptoms, specifically the perspiration and weakness, would worsen around meal-times. These symptoms were associated with abnormally low glucose readings as low as 40–50 mg/dL. For years, she continued to deal with dyspnea and fatigue symptoms, complaining of exercise intolerance and extreme difficulty getting through shifts at work, which began to affect her quality of life significantly.

It was not until March of 2018 and her first consultation with a cardiologist that the patient was diagnosed with POTS after a positive head-up tilt table test. Additional workup included an echocardiogram that was normal and an event monitor revealing sinus tachycardia that correlated with her symptoms. Her initial treatment plan included both lifestyle modifications and pharmacotherapy. She was instructed to stay hydrated and increase salt intake but found neither of these to be helpful. She was also prescribed propranolol 10 mg twice a day, which was ineffective. In fact, she reported low blood pressures and worsening tachycardia. She was also prescribed compression socks, but quickly discontinued their use owing to significant tingling in the lower extremities and an increased sensation of pressure around her head. She struggled to choose between
**KEY TEACHING POINTS**

- Current treatments for postural orthostatic tachycardia syndrome (POTS) are limited and are geared toward symptom relief. There is no current cure for POTS.
- There has been growing evidence that POTS is an autoimmune phenomenon.
- Adalimumab may be a potential treatment for POTS.

her persistent symptoms and therapy beset with disagreeable side effects.

In December of 2018, our patient was diagnosed with SAS with a confirmatory single-photon emission computed tomography scan. She had a positive antinuclear antibody (ANA) titer (1:640 speckled). Other testing included C3 and C4, anti-DS DNA, anti-cardiolipin, and erythrocyte sedimentation rate, all negative or within normal limits. She was initially started on corticosteroids without much benefit. After that, she began adalimumab therapy in December 2019. On just the first day of treatment, our patient noticed a lower heart rate, from 160 to 150 beats/min, on her heart monitor. The following day, her heart rate stayed in the 140s. On the next day, her rate climbed no higher than 130. In just 2 days following adalimumab initiation, our patient reported no more episodes of tremulousness and perspiration related to food intake, and her glucose readings remained normal. She reported experiencing no palpitations, generalized weakness, or sleep disturbances in 1 week after treatment initiation with adalimumab. During a follow-up visit in April 2020, the patient noted that she could exercise and exert herself more now than she was ever able to previously. While the patient still reported tachycardia on standing, as measured by her wearable heart rate monitor, she stated that her symptoms were still far less noticeable.

To better quantify this, we asked our patient in her own words, “It is just like I just don’t have POTS anymore.” To better quantify this, we asked our patient to fill out a Likert scale for POTS, comparing both the frequency and severity of her symptoms before and after treatment with adalimumab (Table 1). Future direction will include to repeat tilt table testing and to check for autoantibodies against alpha-1 adrenergic receptors to assess the degree of POTS autoimmune condition. In the serum of some patients with POTS, 1 study showed the presence of α1-adrenergic receptor (α1AR) antibodies. These antibodies exerted a partial antagonist effect against the peripheral vasoconstrictive compensation of orthostasis, resulting in an overshooting sympathoneural response to maintain vascular tone. Consequently, this sympathetic response leads to tachycardia via unopposed β1-adrenergic receptor activation. In addition, there were also found to be β1AR and β2AR agonist autoantibodies, further promoting this tachycardia. These findings are not unusual among patients with POTS. It has been shown that a vast majority of POTS patients have a

**Discussion**

We presented a 29-year-old female patient with the cardinal symptom of POTS, a quintessential case of the disease. As stated above, there is growing evidence of POTS as an

| POTS symptoms                      | Severity score Before | After | Frequency score Before | After |
|------------------------------------|-----------------------|-------|------------------------|-------|
| Orthostatic lightheadedness         | 4                     | 3     | 7                      | 2     |
| Difficulty passing stool           | 9                     | 9     | 10                     | 10    |
| Early satiety (feeling full)       | 1                     | 1     | 2                      | 2     |
| Depression                         | 1                     | 1     | 4                      | 3     |
| Problems sleeping                  | 9                     | 9     | 10                     | 10    |
| Swelling                           | 0                     | 0     | 0                      | 0     |
| Ringing of the ears                | 0                     | 0     | 0                      | 0     |
| Visual sensitivity to light        | 8                     | 8     | 1                      | 1     |
| Abdominal pain                     | 4                     | 4     | 1                      | 1     |
| Dry mouth                          | 0                     | 0     | 0                      | 0     |
| Bloating                           | 8                     | 8     | 6                      | 6     |
| Nocturnal urination                | 3                     | 3     | 10                     | 10    |
| Whole-body pain                    | 8                     | 6     | 10                     | 10    |
| Frequent daytime urination         | 8                     | 1     | 8                      | 1     |
| Leg pain                           | 6                     | 5     | 7                      | 6     |
| Extremities change color           | 1                     | 1     | 6                      | 6     |
| Sensitivity to heat and odor       | 8                     | 4     | 8                      | 4     |
| Fainting                           | 0                     | 0     | 0                      | 0     |
| Fatigue                            | 10                    | 7     | 9                      | 6     |
| Orthostatic tachycardia            | 10                    | 6     | 10                     | 10    |
| Numbness and tingling              | 8                     | 3     | 8                      | 3     |
| Facial flushing                    | 1                     | 1     | 1                      | 1     |
| Vertigo                            | 4                     | 3     | 1                      | 1     |
| Hand pain                          | 1                     | 1     | 1                      | 1     |
| Headache                           | 4                     | 4     | 4                      | 4     |
| Blurred vision                     | 0                     | 0     | 0                      | 0     |
| Joint pain                         | 10                    | 6     | 10                     | 9     |
| Muscular weakness                  | 8                     | 8     | 4                      | 4     |
| Shortness of breath                | 9                     | 7     | 8                      | 7     |
| Nausea                             | 1                     | 1     | 1                      | 1     |
| Dry eyes                           | 4                     | 4     | 3                      | 3     |
| Rashes                             | 1                     | 1     | 1                      | 1     |
| Brain fog                          | 7                     | 7     | 5                      | 4     |

POTS = postural orthostatic tachycardia syndrome.

The POTS Likert scale is designed to help quantify both the severity and frequency of POTS symptoms before and after treatment with adalimumab. The scoring is a numerical value between 0 and 10. With regard to frequency, the scoring is as follows: 0 = never, 1 = once a month or less, 2 = 1–3 times a month, 3 = once a week, 4 = a few times a week, 5 = most days, 6 = once a day, 7 = a few times per day, 8 = most of the time, 9 = nearly constantly, 10 = constantly, without exception. With regard to severity, the scoring is as follows: 0 = nonexistent, 1 = very mild, 2 = rather mild, 3 = mild, 4 = low-moderate, 5 = moderate, 6 = high-moderate, 7 = starting to be severe, 8 = severe, 9 = extremely severe, 10 = most severe possible.
serum containing at least 1 adrenergic g-protein-coupled receptor antibody. These antibodies may even possess the ability to alter the severity of the disease, as the levels of some g-protein-coupled receptor antibodies were positively correlated with symptom severity. Despite mounting evidence supporting the widespread applicability of immunomodulatory therapy in POTS, attempts to utilize this avenue of medical management are still not well documented.

Our patient’s POTS symptoms were refractory to traditional medical management and remained untreated until initiation of adalimumab pharmacotherapy for her SAS. Adalimumab is a human IgG1 monoclonal antibody against tumor necrosis factor (TNF)-alpha administered subcutaneously. The blockage of TNF-alpha has a complexity of downstream consequences, including inhibition of leukocyte-mediated synthesis and release of cytokines, chemokines, and other proinflammatory modulators imperative to the pathophysiology of autoimmune disease. Ironically, several conditions currently managed with adalimumab were found to be susceptible to the drug serendipitously, as primary treatment for 1 condition led to unintended therapeutic side effects for another. Such is the case here, as the lightheadedness, fatigue, palpitations, dyspnea, and weakness experienced by our patient for years were resolved within months following the initiation of adalimumab therapy for joint pain and stiffness associated secondary to SAS. Because the autoimmune nature of POTS is suspected to be related to adrenergic autoantibodies, it is possible that upstream inhibition of TNF-alpha alters the levels and activity of these antibodies, attenuating the inflammatory response that induces symptoms. Although the exact mechanism behind the treatment’s efficaciousness must be further studied, we present one of the first recorded alleviations of POTS using immunomodulatory therapy.

The establishment of POTS as an autoimmune condition continues to be developed. Owing to the propensity for several autoimmune conditions to occur in patients simultaneously, further data could be gathered regarding POTS and its prevalence as a comorbidity with other autoimmune diseases. Routine serum analysis for antiadrenergic antibodies could also play a role moving forward, starting with our patient. In conjunction, these could reinforce POTS as an autoimmune condition and promote immunomodulatory therapy as a primary treatment modality.

**Conclusion**

There is growing evidence to suggest POTS is an autoimmune disorder. We presented a patient with a history of POTS who underwent treatment with adalimumab for SAS. Interestingly, virtually all of the patient’s POTS symptoms were resolved after treatment initiation with adalimumab. This case report further reinforces the hypothesis that POTS is autoimmune. Much larger human research studies are needed to further our understanding of POTS’s autoimmune nature and the role immunomodulator therapy can play in managing this debilitating disease.

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