Systemic Pain Relief after Omalizumab Injection in Patient with Hypermobile Ehlers Danlos Syndrome: A Case Report

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Treating pain in patients with hypermobile Ehlers Danlos Syndrome (hEDS) is complex and must be addressed in a multidisciplinary fashion. Patients tend to experience diffuse, chronic, debilitating pain. Pain is described as both nociceptive and neuropathic in nature and is frequently systemic in presentation. We present a case of a 33-year-old female patient with severe pain, resulting in significant functional decline, impaired quality of life, and severe isolation due to her underlying hEDS and related medical comorbidities. This patient has a past medical history of chronic regional pain syndrome (CRPS), gastroparesis, small fiber neuropathy, ureteral stones, depression, and fibromyalgia. She follows with the Physical Medicine and Rehabilitation (PM&R) clinic for ongoing treatment of hEDS and comorbid conditions (Mast Cell Activation Syndrome [MCAS] and Postural Orthostatic Tachycardia Syndrome [POTS]) with the goal of improved strength, mobility, and quality of life.

Despite many treatment trials, both pharmacologic and non-pharmacologic in nature, the patient's chronic systemic symptoms remained uncontrolled. The PM&R team was further limited on additional pharmacologic treatments due to her significant allergy history including gabapentin, zolpidem, ramelteon, duloxetine, eszopiclone, pregabalin, sulfamethoxazole-trimethoprim, clonidine, cortisone, erythromycin, melatonin, nortriptyline, ropinirole, and trazodone. From a non-pharmacological perspective, the patient was trialed on an anti-inflammatory diet but failed due to comorbid gastroparesis. The patient was unable to complete physical and cognitive behavior therapies due to pain limitations and financial concerns. The PM&R team continuously faced a vicious cycle of a patient desperate for help, trialing a range of treatment modalities, and having to abruptly stop due to medical and financial limitations.

In January of 2023, a breakthrough in this cycle was noted once the patient began receiving omalizumab injections with the Allergy and Immunology clinic for her MCAS. Omalizumab is a monoclonal antibody that binds to IgE receptors on mast cells and basophils to prevent an immune-mediated reaction [1]. After receiving five injections, the patient reported a significant improvement in the inflammation throughout her body, with additional profound reduction in her systemic swelling. Subsequently, the patient noticed a decrease in systemic pain and significant increase in functional mobility.

The patient continues to follow with the PM&R department and has maintained an overall reduction in limiting systemic symptoms and chronic pain. This has been tracked with the visual analog scale at each appointment. Pre-omalizumab treatment pain was recorded as 10/10. Post- omalizumab treatment pain has consistently been recorded as 6-7/10. As noted in literature, a 3-point reduction is a clinically significant outcome correlating to patient perception of sufficient pain control [2]. While Omalizumab has been beneficial in decreasing systemic inflammation and pain, this most importantly has led to an increase in the patient's functional mobility and independence, which were her primary goals when presenting to the PM&R clinic.

Ultimately, the reduction in this patient's systemic inflammatory symptoms and chronic pain after initiating omalizumab therapy prompted the question of possible links between antihistamines, omalizumab, and

chronic pain relief. A literature search was conducted and to the author's knowledge, there is no prior literature researching this connection.

Pain is a hallmark of inflammation, and there is considerable evidence that suggest that mast cells play a role in pain signaling by secreting mediators that induce peripheral sensitization. Targeting mast cell activation and production may improve analgesic therapy for systemic mast cell activation disease [3]. Currently, omalizumab is approved for use in cases of mast cell activation syndrome, urticaria, and severe allergic asthma [4, 5].

In patients with hEDS, uncontrolled, diffuse, atypical pain is often the presenting symptom and most difficult to treat. While there are multiple factors that potentially contribute, including nociceptive pain, neuropathic pain, impaired proprioception, and central sensitization, the mechanism behind pain in EDS and its subtypes is poorly understood [6]. Therefore, there are no disease-modifying treatments available for EDS, rather management is tailored to the patient's symptomatology [7]. Current methods in practice include physiotherapy, pharmacologic pain management, and lifestyle modifications, including limited vigorous activity to decrease bone and muscle morbidity [8, 9].

In addition, the role of the immune system in any of the EDS subtypes is not well known. Few case reports suggest a possible association between hEDS, allergies, and immunodeficiencies; however, further research is required to better understand the correlation [10]. In addition to the commonly observed rheumatological manifestations of hEDs, such as joint instability, arthralgias, myalgias, and arthritis, many patients with hEDS have comorbid systemic inflammatory disorders that could be explained by a chronic release of mast cell-related immune factors [11]. Mast cells are known to express IgE and IgG receptors, among several others, that release proinflammatory granule mediators like histamine upon binding. When unregulated, as seen in hEDS, these mediators can affect any organ system and present with a range of clinical manifestations, including IBS, urticaria, hypotension, cardiac arrhythmias [4, 12].

Our patient with hEDS and MCAS showed significant improvement in her chronic systemic pain after omalizumab. Though omalizumab can be used to treat comorbidities of hEDS, we propose there may be some use in considering further research in applying omalizumab as a potential therapy in hEDS patients with uncontrolled systemic pain. Further research can evaluate the relationship between omalizumab and pain in hEDS more closely. With the potential for omalizumab to reduce pain in hEDS, patients could integrate this therapy into their regiment sooner, with the hope to improve overall outcomes in terms of pain, mobility, functionality, social interaction, and quality of life.

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