Hypereosinophilic Syndrome With Sialadenitis and Orbital Inflammation: A Case Report

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Palabras clave: Síndrome de hipereosinofilia. Inhibidor de IL-5. Sialadenitis. Inflamación orbitaria.

We report the case of a 77-year-old white female presenting with a 2- to 3-day history of sudden-onset face and neck swelling. Her past medical history included asthma and chronic sinusitis. Our initial suspicion was angioedema, for which we started oral prednisone and referred her to an ENT clinic. Within 2 days of treatment, the swelling had improved remarkably. In the review of systems, the patient reported no fever, weight loss, trauma, or acute respiratory complaints. Furthermore, she had not recently started any new herbal or nutritional supplements.

Vital signs were within normal limits. The clinical examination was notable for a puffy face with enlarged, nontender bilateral parotid and submandibular glands and a slightly enlarged tongue with some ulcers. Both pupils were round and reactive to light and accommodation. Visual acuity was normal in both eyes. The systemic examination, including pulmonary, cardiac, abdominal, and neurologic findings, was unremarkable.

The initial laboratory work-up comprised a complete blood count (CBC) with differentials, complete metabolic panel (CMP), C-reactive protein (CRP), complement levels, C1-esterase-inhibitor activity, antinuclear antibody (ANA), and anti-SSA and anti-SSB antibodies. Computed tomography (CT) of the neck and chest and magnetic resonance imaging of the orbit were scheduled.

The initial laboratory results were notable for eosinophilia with an absolute eosinophil count (AEC) of 2700/µL, borderline white blood cell count of 10.6 × 10^9/L, and negative findings for complement, C1 esterase, ANA, and anti-SSA/SSB, as well as borderline CRP (12). At this point, the patient was started on oral prednisone 30 mg daily, and more laboratory tests were requested, including stool for ova and parasites, *Strongyloides* antibody, tryptase level, and assessment of the *FIP1L1-PDGFRA* rearrangement/mutation.

The CBC was repeated after 3-4 weeks, revealing an AEC of 816 and a normal white blood cell count of 7.7 × 10^9/L. Given the improvement in symptoms, a repeat CBC was planned the following month, along with office follow-up. The assessment revealed an AEC of 4850/µL and elevated white blood cell count of 14.1 × 10^9/L. At that point, we decided to start the IL-5 inhibitor, mepolizumab.

A repeat CBC revealed an AEC of 100/µL and white blood count of 9.2 × 10^9/L. All symptoms, including the ophthalmologic symptoms, resolved completely.

Of note, the neck CT scan was deemed clinically unnecessary given the good clinical response to prednisone. The chest CT scan revealed previously known scattered pulmonary nodules. Magnetic resonance imaging of the orbits revealed findings consistent with orbital inflammatory disease including left posterior scleritis, perineuritis, and adjacent cellulitis and myositis of the extraocular muscles. The ophthalmologist prescribed prism glasses to correct diplopia, which was considered to be secondary to orbital muscle and soft tissue inflammation. Soon after initiation of mepolizumab, all symptoms, including visual symptoms, had completely resolved, and prism glasses were not needed.

The patient has continued to receive monthly mepolizumab injections for the past 1-2 years and has been doing well, with no subsequent clinical problems or reactions, until the most recent office follow-up earlier this year. The patient

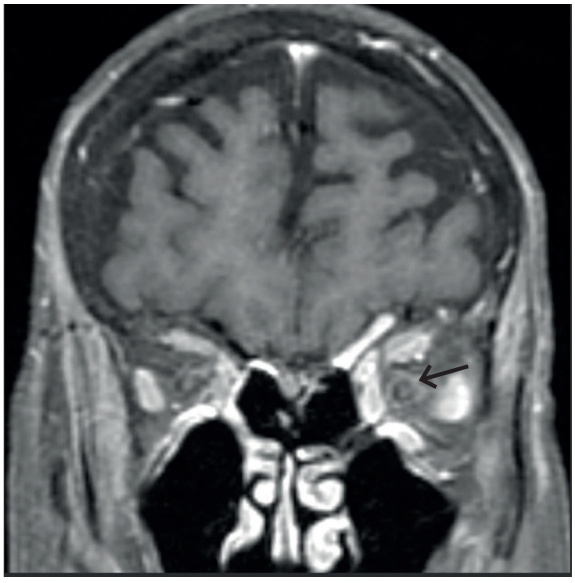

Figure. Magnetic resonance image showing left optic neuritis (arrow).

gave her written informed consent for the publication of this case report.

Hypereosinophilic syndrome (HES) involves various organ systems, mainly the dermatologic, cardiovascular, pulmonary, hematopoietic, and nervous systems, as well as, albeit less commonly, the renal and hepatic systems. However, in recent years, more diverse clinical features and wider organ system involvement have been described. We report discernible facial, neck, and tongue swelling (related to an enlarged parotid and submandibular and sublingual salivary glands) and diplopia (related to orbital inflammation) as presenting manifestations of HES, as well as an excellent response to mepolizumab, which is an approved treatment for HES. Mepolizumab has also proven effective in chronic rhinosinusitis with nasal polyposis [1] and in reducing asthma exacerbations [2].

The few case reports on ocular involvement in HES are related mostly to retino-choroidal vascular involvement [3] or conjunctivitis [4]. In another case, the patient presented with torticollis and proptosis [5]. However, the uniqueness of the case we report is the initial presentation of HES with sialadenitis and the fact that the patient was an adult with extensive periorbital inflammatory changes (including optic neuritis affecting vision [Figure]) and a very good response to mepolizumab. The absence of tissue biopsy or histology or serum IgG levels prevented us from ruling out other eosinophilic diseases, such as IgG4-related disease, eosinophilic fasciitis [6], and eosinophilic granulomatosis with polyangiitis. Eosinophilic fasciitis seems unlikely in the present case given the lack of pain symptoms, and eosinophilic granulomatosis with polyangiitis is also unlikely given the absence of fever and other systemic symptoms. Nonetheless, the approaches to management of these conditions do overlap.

HES encompasses a rare and complex group of heterogenous disorders characterized by persistently and substantially elevated eosinophil levels and mediators leading to tissue inflammation and damage. The age-adjusted incidence of HES ranges between 0.16 and 0.36 per 100 000, and the incidence ranges between 0.36 and 6.3 per 100 000 [7]. The disease most commonly occurs between the ages of 20 and 50 years, although it has also been diagnosed in children and in older persons (as in the present case).

The pathophysiology of HES is related to the proinflammatory, prothrombotic, and profibrotic properties of eosinophils, which infiltrate organs, resulting in end-organ dysfunction. IL-5 is the key cytokine mediating the differentiation of eosinophils in bone marrow and the maturation and activation of eosinophils. Even without an eosinophilic mediator or cytokine profile in the present case, the prompt response to mepolizumab indicates that HES was the predominant pathophysiology.

Evaluation and diagnosis involve a focused history, basic laboratory tests (including CBC, CMP, troponin, screening for parasitic infections, and investigating potential drug reactions), and allergies. The *FIP1L1-PDGFRA* mutation may be associated and should be ruled out. Imaging, including ECG, chest/abdomen imaging, and echocardiogram should be considered, as should tissue biopsy.

Management includes identifying and treating underlying drug hypersensitivity and helminth infestation. If these are ruled out, therapy with systemic corticosteroids and immunomodulatory agents such as mepolizumab should be evaluated. Alternative medications such as tyrosine kinase inhibitors (imatinib), hydroxyurea, and interferon-α have been used successfully in HES, especially in refractory cases.

The mechanisms for partial response or nonresponsiveness to IL-5 inhibitors include alternative pathways for eosinophil activation such as IL-4, IL-13, granulocyte-macrophage colony-stimulating factor, and IL-3, as well as mutations in eosinophil or IL-5 receptor signaling. In such cases, other targeted treatments, such as dupilumab (targeting IL-4 and IL-13) or alternative treatments, such as those mentioned above, could be successful. A case of HES associated with regulatory T-cell disruption as a complication of stem cell transplantation has been reported [8].

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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