



Case report

Dysphonia and dyspnea in idiopathic hypereosinophilic syndrome treated with Mepolizumab

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A B S T R A C T

Hypereosinophilic syndrome (HES) is characterized by a persistently elevated eosinophil count associated with eosinophil-related end-organ damage and thromboembolic events, in the absence of an identifiable cause. We present a case of idiopathic HES with evidence of peripheral and tissue eosinophilia while on high dose prednisone, associated with muscle tension dysphonia, colitis, and jackhammer esophagus. The patient was treated with the interleukin-5 inhibitor, Mepolizumab, with resolution of symptoms including dyspnea, diarrhea and dysphonia.

1. Introduction

Hypereosinophilic syndrome (HES) is characterized by a persistently elevated eosinophil count associated with eosinophil-related end-organ damage and thromboembolic events, in the absence of an identifiable cause [1]. We present a case of idiopathic HES treated with the interleukin-5 (IL-5) inhibitor, Mepolizumab, with resolution of symptoms including dyspnea and dysphonia.

2. Case report

A 73-year-old woman presented with a three-year history of dyspnea on exertion, chest tightness, and dysphonia (Video 1). Over the course of three years she had peripheral eosinophilia ranging from 1128–1907 cells/uL while on 40 mg prednisone daily. Her medical history was relevant for unprovoked venous thromboembolic disease and Jackhammer esophagus. Her workup prior to presentation to our clinic included a bronchoscopy without evidence of eosinophilia on bronchoalveolar lavage, as well as a negative work up for connective tissue disease, vasculitis and parasitic infection. Regarding her dysphonia, she had been evaluated by neurology and Otorhinolaryngology and diagnosed with idiopathic muscle tension dysphonia, and noted to have worsening of dysphonia while off steroids. She was trialed on bronchodilators and inhaled steroids without improvement in symptoms. Malignancy was ruled out through Fluorescence in situ Hybridization (FISH) evaluating for FGFR1, FIP1L1-PDGFR, PDGFRB, and CBF/ MYH11 rearrangements that have been associated with HES. Based on her eosinophilia while on high dose steroids, history of

thromboembolic disease, negative workup, and tissue hypereosinophilia on dermatology biopsy that showed superficial perivascular dermatitis with many eosinophils (Fig. 1) as well as mild eosinophilia on colon biopsy (Fig. 2), the patient was diagnosed with idiopathic hypereosinophilic syndrome. She was taken off steroids and started on Mepolizumab, dosed at 100mg subcutaneous every 4 weeks. After 3 doses, she experienced significant improvement in her symptoms of dyspnea and chest tightness with complete resolution of her dysphonia (Video 2).

Supplementary video related to this article can be found at <http://dx.doi.org/10.1016/j.rmcr.2018.05.013>.

3. Discussion

Persistent peripheral eosinophilia and end organ damage that is seen in HES may occur as a result of a myeloproliferative variant of the hypereosinophilic syndrome, or more commonly due to maturation, differentiation and mobilization of eosinophils from hematopoietic progenitors due to the influence of IL-5 [2–4]. Traditional diagnostic criteria for the diagnosis of HES would follow Chusid's criteria requiring an eosinophil count of > 1500 cells per ml in the absence of steroids, present for greater than 6 months, with evidence of end-organ damage and absence of other causes of eosinophilia [5]. However, in patients that require chronic steroids for symptom control, diagnosis is more challenging and requires a tailored approach with a focus on ruling out more common diagnosis.

Malignancy can be ruled out as the cause of the peripheral eosinophilia through Fluorescence in situ Hybridization (FISH) testing. The

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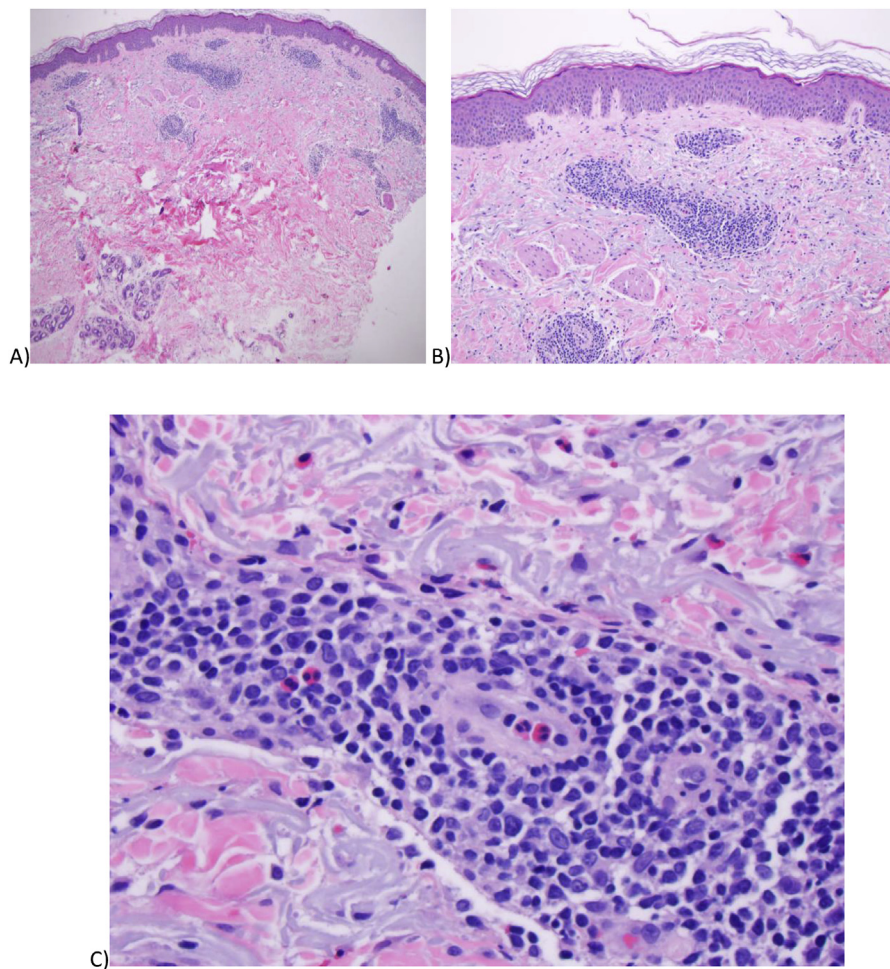


Fig. 1. A-C. Skin punch biopsy revealed multifocal perivascular mononuclear and eosinophilic inflammation in the superficial dermis, features of superficial perivascular dermatitis. There is neither evidence of vasculitis nor granuloma in this biopsy.

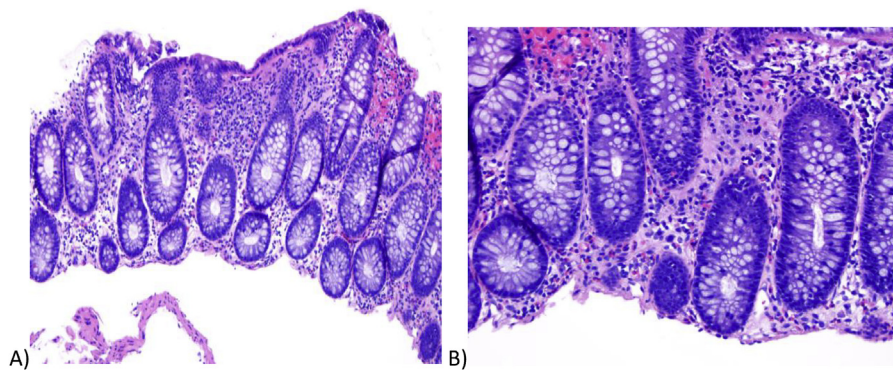


Fig. 2. A-B. The biopsy from the colon demonstrated loss of surface epithelial mucin and mild eosinophilia in the deep portion of the lamina propria. Rare crypts are also focally infiltrated by eosinophils.

absence of allergic eosinophilia should be ruled out based on negative allergen testing and infectious etiology can be ruled out with negative testing for ova and parasites. A bronchoalveolar lavage evaluation can be used to evaluate for eosinophilic predominance in order to rule out the diagnosis of eosinophilic pneumonia. Furthermore, biopsy evidence of extravascular eosinophilia serves to support a systemic process.

In regard to the presentations with dysphonia and Jackhammer esophagus; there have been many studies showing peripheral eosinophilia as a cause of neuropathy [6,7]. These conditions have never before been linked to HES, however the physiology of neuropathy due to

hypereosinophilia and the pathophysiology of these conditions seem to suggest a relationship [8,9].

The most difficult diagnosis to evaluate in most patients with HES is the possibility of ANCA negative Churg Strauss Syndrome (CSS) in the eosinophilic phase. There is considerable overlap between the phenotypic presentation of patients with HES as compared to patients who meet the American College of Rheumatology criteria for diagnosis of Churg Strauss [10]. Multiple studies have been done to study methods to differentiate CSS from HES [11–13]. Biomarkers such as serum levels of cytokines, cytokine receptors and chemokines, have been studied,

and to this date no marker has been identified to reliably differentiate between the two syndromes [14]. At this point, the development of vasculitis on biopsy serves as the only definitive difference between HES and ANCA negative CSS. Literature shows that the development of vasculitis in CSS can vary from 6 months to 2 decades after initial symptoms, and hence the absence of vasculitis at the time of evaluation cannot be used as definitive proof as to the absence of a connective tissue process [15].

Mepolizumab, a humanized anti-interleukin 5 monoclonal antibody, reduces eosinophil counts in blood and tissues by blocking interleukin-5, an activating eosinophil cytokine, through binding to eosinophil surface receptors [16].

There have been multiple studies evaluating the role of Mepolizumab in obstructive lung disease. It is suggested that decrease in airway inflammation serves as the main pathophysiology in improvement of respiratory symptoms [17]. Anti-interleukin 5 monoclonal antibody has never been described in resolving other systemic symptoms such as muscle tension dysphonia that can be related to eosinophilic neuropathy, or eosinophilic colitis.

Although treatment with Mepolizumab has been shown to be effective in a variety of eosinophilic diseases, there are limited studies on long-term use of the treatment. At this time, FDA approval has not been established for the use of Mepolizumab in the treatment of HES.

Disclosures

All authors have no disclosures of note.

Contributions

DK, AA, XL, JA and DU all contributed to the drafting and writing of this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmcr.2018.05.013>.

References

- [1] A.D. Klion, B.S. Bochner, G.J. Gleich, et al., Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report, *J. Allergy Clin. Immunol.* 117 (2006) 1292–1302.
- [2] H.H. Kariyawasam, D.S. Robinson, The eosinophil: the cell and its weapons, the cytokines, its locations, *Semin. Respir. Crit. Care Med.* 27 (2006) 117–127.
- [3] M.E. Rothenberg, S.P. Hogan, The eosinophil, *Annu. Rev. Immunol.* 24 (2006) 147–174.
- [4] M.E. Rothenberg, et al., Treatment of patients with the hypereosinophilic syndrome with Mepolizumab, *N. Engl. J. Med.* 358 (2008) 1215–1228.
- [5] M.J. Chusid, C.D. Dale, B.C. West, S.M. Wolff, The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature, *Medicine (Baltim.)* 54 (1975) 1–27.
- [6] D.T. Durack, S.M. Sumi, S.J. Klebanoff, Neurotoxicity of human eosinophils, *Proc. Natl. Acad. Sci. U. S. A.* 76 (3) (1979 Mar) 1443–1447.
- [7] M. Moore Patricia, et al., Neurologic dysfunction in the idiopathic hypereosinophilic syndrome, *Ann. Intern. Med.* 102 (1985) 109–114.
- [8] L. Dorfman, et al., Neuropathy in the hypereosinophilic syndrome, *Muscle Nerve* 6 (1983) 291–298.
- [9] F.D. Loo, et al., Multiphased esophageal peristaltic pressure waves in patients with diabetic neuropathy, *Gastroenterology* 88 (2) (1985 Feb) 485–491.
- [10] A.T. Masi, G.G. Hunder, J.T. Lie, B.A. Michel, D.A. Bloch, W.P. Arend, L.H. Calabrese, S.M. Edworthy, A.S. Fauci, R.Y. Leavitt, et al., The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis), *Arthritis Rheum.* 33 (8) (1990 Aug) 1094–1100.
- [11] T. Dallos, G.R. Heiland, J. Strehl, T. Karonitsch, W.L. Gross, F. Moosig, et al., CCL17/thymus and activation-related chemokine in Churg-Strauss syndrome, *Arthritis Rheum.* 62 (11) (2010) 3496–3503.
- [12] P. Guilpain, J.F. Auclair, M.C. Tamby, A. Servettaz, A. Mahr, B. Weill, et al., Serum eosinophil cationic protein: a marker of disease activity in Churg-Strauss syndrome, *Ann. N. Y. Acad. Sci.* 1107 (2007) 392–399.
- [13] K. Polzer, T. Karonitsch, T. Neumann, G. Eger, C. Haberler, A. Soleiman, et al., Eotaxin-3 is involved in Churg-Strauss syndrome—a serum marker closely correlating with disease activity, *Rheumatology* 47 (6) (2008) 804–808.
- [14] Khoury Paneez, et al., Serum biomarkers are similar in Churg-Strauss syndrome and hypereosinophilic syndrome, *Allergy* 67 (9) (2012 September) 1149–1156.
- [15] J.G. Lanham, Churg-Strauss syndrome, *Br. J. Hosp. Med.* 47 (9) (1992 May 6–19) 667–673.
- [16] C. Büttner, A. Lun, T. Splettsöesser, G. Kunkel, H. Renz, Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions, *Eur. Respir. J.* 21 (2003) 799–803.
- [17] H. Ortega, et al., Mepolizumab treatment in patients with severe eosinophilic asthma, *NEJM* 371 (2014) 1198–1207.