

**“Allergy does occur in the urinary tract, is frequently unrecognized, and generally mistreated.”**<sup>1</sup> So begins an article in the Journal of Urology by Kindall and Nickels published in 1949. In the 70 years since then, much remains the same. Eosinophilic cystitis (EoC) is a form of interstitial cystitis characterized by eosinophilic infiltration of the bladder wall. It could be loosely construed as “allergy” in the urinary tract. It was first specifically described by Edwin Brown in 1960.<sup>2</sup> EoC is a rare condition. A PubMed search under the term eosinophilic cystitis from 2003 to present yielded 93 citations; furthermore, there are probably no more than 200 cases reported in the English literature. As with other forms of interstitial cystitis, it can lead to significant morbidity<sup>3</sup> and quality of life (QoL) impairment. Urinary frequency and urgency can be debilitating in some cases, with dysuria, incontinence, hematuria, and pelvic pain as common presenting symptoms.<sup>4</sup> The etiology of EoC is for the most part unknown, although some reports have been ascribed to medications, infection, bladder trauma, or hypereosinophilic syndrome. Due to the rarity of this condition, most of the literature is restricted to small case studies or single case reports. A large pooled analysis of 135 cases published in 2000 found peripheral eosinophilia in 43% of cases and positive urine cultures in 26% of patients.<sup>5</sup> Currently there is no consensus about EoC treatment.<sup>4</sup> Symptomatic management has consisted of oral and intravesical corticosteroids, antihistamines, antispasmodics, antibiotics, leukotriene antagonists, immunosuppressives, and in severe cases, surgical intervention.<sup>4,5,6</sup>

The treatment of eosinophilic disorders has recently been revolutionized by the arrival of monoclonal antibodies (mAbs) directed at interleukin-5 (IL-5), a chemotactic cytokine for eosinophils. These agents have been FDA approved for the treatment of asthma and eosinophilic granulomatous polyangiitis, but other investigations are ongoing for other eosinophilic disorders such as eosinophilic esophagitis.<sup>7</sup> Busse et al. mentioned EoC as a possible candidate for anti-IL-5 mAbs in 2010, but to our knowledge, no studies have been reported for this condition.<sup>8</sup> We hypothesize that the IL-5 receptor blocker, benralizumab, may be an effective treatment for EoC by reducing eosinophilic infiltration of the bladder and improving QoL.

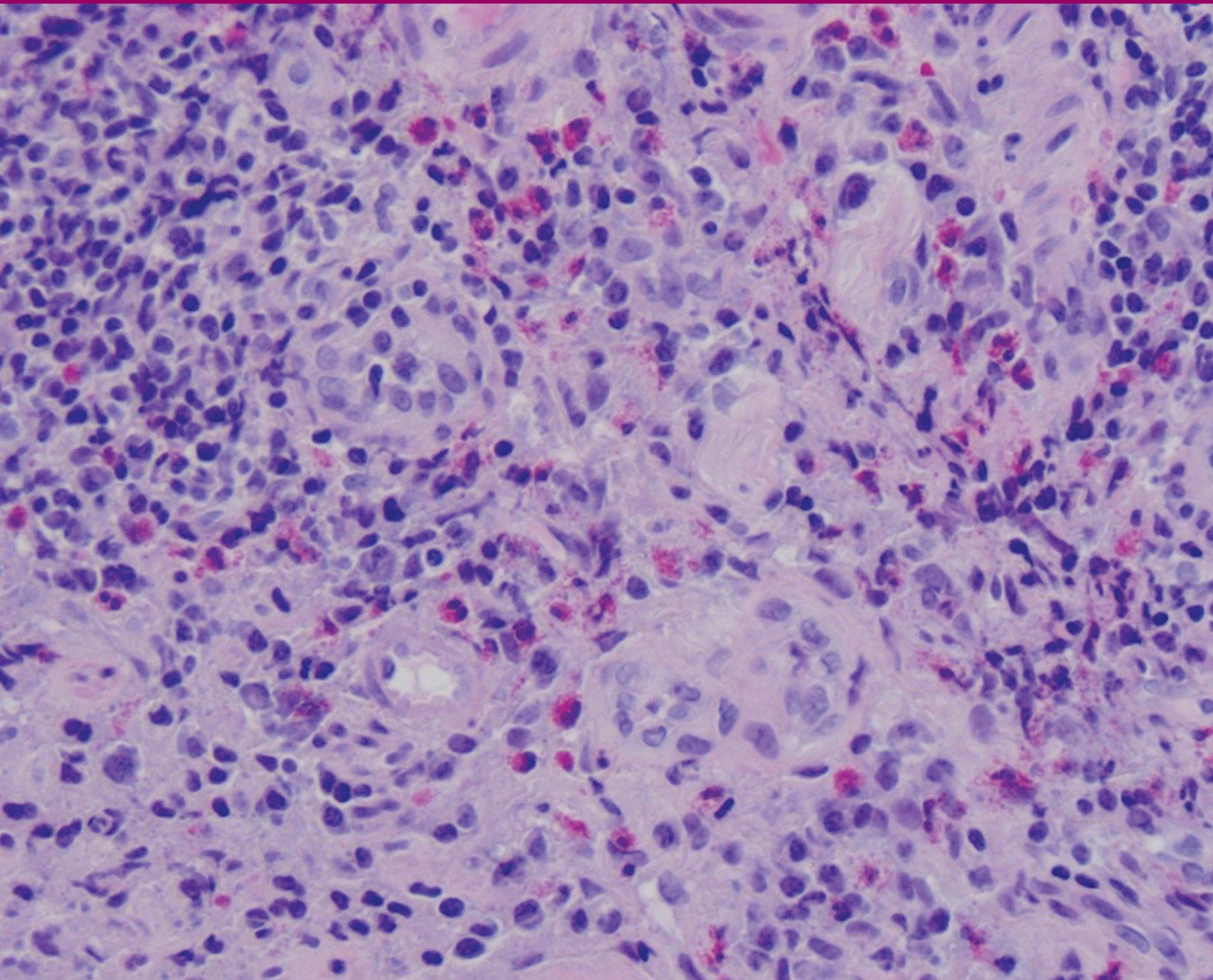
Methods

We report here the case of a 78-year-old woman referred to the allergy/immunology practice by her urologist in the summer of 2019. She had a two-year history of extreme dysuria, urgency, frequency, incontinence, pelvic pain, and hematuria. Notably, her symptoms included painful voiding every 20 minutes during the day and up to 20 times at night. This resulted in severe sleep disruption, subsequent depression, and social disturbance. She was essentially homebound. The patient had a long urologic history. A right nephrectomy was performed in 1997 for renal cell carcinoma. Subsequently, she was treated for recurrent urinary tract infections and interstitial cystitis. CT imaging done in January 2019 demonstrated bladder wall thickening of 8mm at the fundus. A bladder biopsy was performed February 2019, and the bladder wall was found to have eosinophilic infiltrates at up to 100 eosinophils/high power field (fig 1). She had no peripheral eosinophilia. When seen initially in the allergy clinic in May 2019, her skin prick tests were negative for inhalants and common allergenic foods. Previous pharmacologic treatments included oral corticosteroids, antihistamines, monteleukast, antispasmodics, antibiotic suppressive therapy and antibiotic treatment when indicated by dipstick and culture results. Despite these interventions, her symptoms were unrelieved and her self-reported QoL continued to diminish. We administered a validated questionnaire instrument, the Urogenital Distress Inventory (UDI-6) short form<sup>9</sup> and found her pretreatment scores to be markedly elevated at 58. Following informed consent for off-label use of a biologic intervention benralizumab (kindly provided by Astra Zeneca as samples), the patient was started at 30mg subcutaneously every four weeks in May 2019. The patient has been followed monthly to assess clinical response.

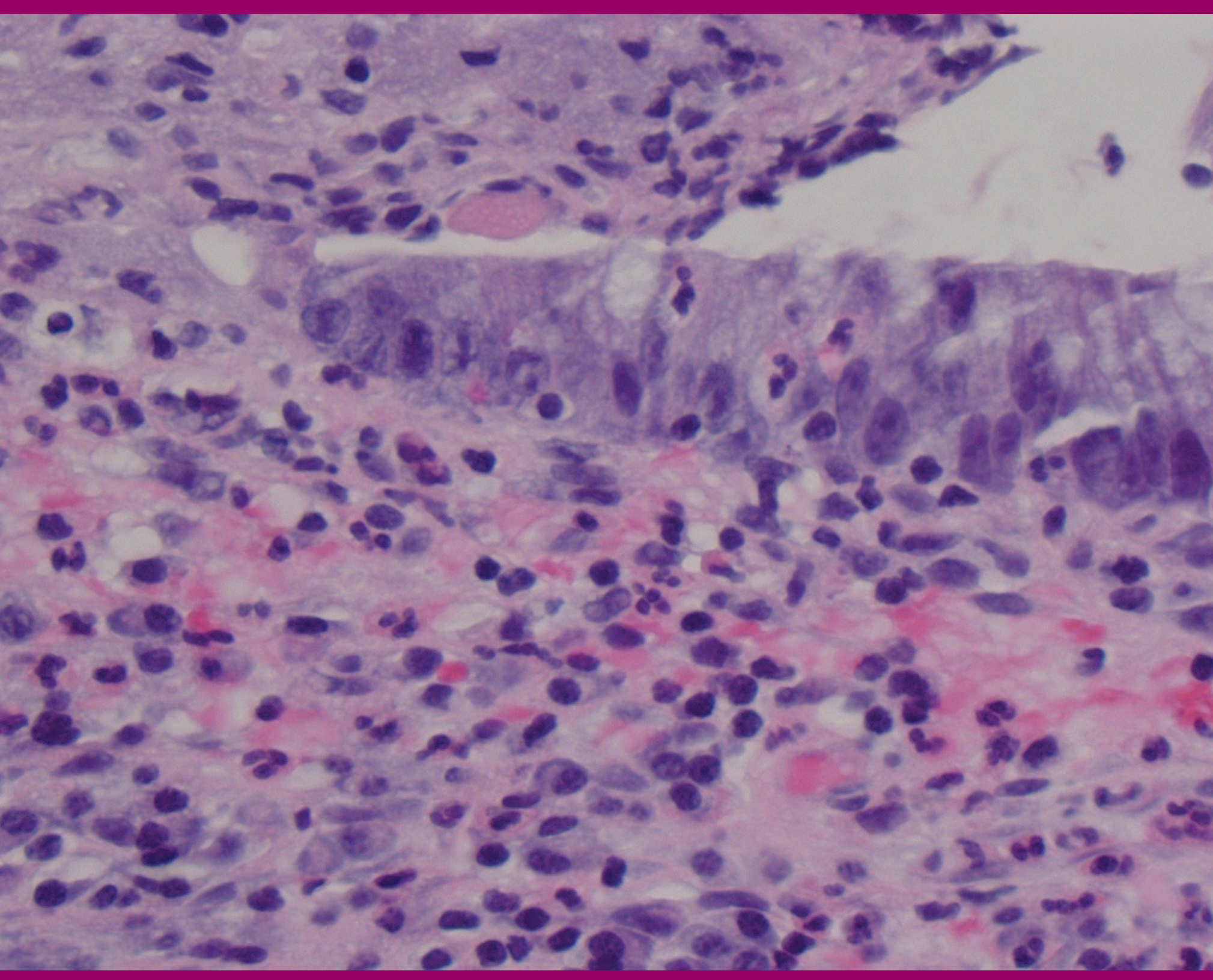
# Eosinophilic Cystitis Treatment with Benralizumab

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100% Reduction in eosinophils  
Up to 65% improvement in QoL



Bladder biopsy from February 2019 showing numerous eosinophils and eosinophilic microabcess.



Bladder biopsy from January 2020 showing urothelium and continued cystitis but no eosinophils.

Results

Following the third dose, the patient’s UDI-6 score was reduced to 20, demonstrating a 64% improvement in her subjective symptoms and QoL. The daytime voiding interval increased to three hours and her sleep disruption was significantly improved to 4 to 8 nocturia events per night. She reported no longer feeling “hopeless and housebound.” No side effects from the benralizumab were noted. Three separate urine cultures obtained during the summer months were positive for group B strep and Klebsiella species. These were treated with appropriate antibiotics. Her urinary frequency increased during these infections, but subsequently decreased again with antibiotic therapy. Antispasmodics have been continued. Voiding diaries and patient reports demonstrate that urinary frequency and incontinence events begin to increase about three weeks after each benralizumab injection. As of December 2019, the urine has remained sterile, and she continues to void between 4 and 8 times at night. A repeat biopsy was obtained in January 2020. The biopsy showed continued cystitis, but only rare eosinophils were seen (fig.2) After the eleventh dose, the UDI-6 total score was 38, which demonstrates a 34% improvement in the patient’s QoL, when compared to the pretreatment score.

Discussion

EoC is an orphan disease. We describe the successful use of the IL-5 receptor antagonist, benralizumab, in our patient with EoC. She had both improved QoL as measured by the UDI-6, symptomatic relief, and histologic resolution of her eosinophilic infiltration. We believe this is the first report of the use of the biologic benralizumab in this condition. In the pooled analysis of 135 patients by Van den Ouden, only 66% of EoC patients responded to treatment as defined as a complete absence of urinary symptoms.<sup>5</sup> Since the publication of this large analysis in 2000, there have been no significant changes in the therapeutic approach, and the literature remains mostly relegated to sporadic case reports. Our patient demonstrates the possibility that biologic intervention with IL-5 antagonists may be a new paradigm in the treatment of EoC, and one that ideally should be further addressed in formal clinical trials.

The use of benralizumab samples in this off-label case is problematic. FDA approval requires careful clinical trials to ascertain safety and efficacy before releasing a biologic to patients. Such trials are expensive, and require large patient populations and considerable statistical expertise. Pharmaceutical companies understandably have a significant investment in bringing such medications to market. In the case of orphan diseases such as EoC, there may be no practical way to investigate interventions simply due to its rarity. There is in fact, no current clinical trial investigating this disease.

In summary, what treatment options for this patient remained when virtually all other treatment modalities have been exhausted? As physicians and nurses, our ethical goal is to relieve suffering, while doing no harm. This patient was clearly suffering an immense physical and psychosocial burden due to her EoC disease process. This report demonstrates a positive clinical and histologic result, which warrants further investigation and research.

References

1. Kindall L, Nickels T. Allergy of the pelvic urinary tract in the female: A preliminary report. J Urol. 1949;6(2):222. doi: 10.1016/S0022-5347(17)69057
2. Brown EW. Eosinophilic granuloma of the bladder. J Urol. 1960;83:665-8.
3. Marcu I, Campian E, Tu, F. Interstitial cystitis/bladder pain syndrome. Semin Reprod Med. 2018;36:123-135. doi: 10.1055/s-0038-1676089
4. Mosholt KS, Dahl C, Azawi, NH. Eosinophilic cystitis: Three cases, and a review over 10 years. BMJ Case Reports. 2014 Oct 13. doi: 10.1136/bcr-2014-205708
5. Van den Ouden D. Diagnosis and management of eosinophilic cystitis: A pooled analysis of 135 cases. Eur Urol. 2000 Apr;37(4):386-94. doi: 10.1159/000020183
6. Aleem S, Kumar B, Fasano MB, Takacs E, Azar AE. Successful use of cyclosporine as treatment for eosinophilic cystitis: A case report. World Allergy Organization Journal. 2016;9:22. doi: 10.1186/s40413-016-0113-4
7. Harish A, Schwartz SA. Targeted anti-IL-5 therapies and future therapeutics for hypereosinophilic syndrome and rare eosinophilic conditions. Clin Rev Allergy Immunol. 2020 Jan 9. doi: 10.1007/s12016-019-08775-4
8. Busse WW, Ring J, Huss-Marp J, Kahn JE. A review of treatment with mepolizumab, an anti-IL-5 mAb, in hypereosinophilic syndromes and asthma. J Allergy Clin Immunol. 2010 Apr;125(4):803-13. doi: 10.1016/j.jaci.2009.11.048
9. Naughton MJ, Donovan J, Badia X, Corcos J, Gotoh M, Kelleher C, Lukacs B, Shaw C. Symptom severity and qol scales for urinary incontinence. Gastroenterology. 2004 Jan;126(1 Suppl 1):S114-23. doi: 10.1053/j.gastro.2003.10.059

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