

## Efficacy of mepolizumab for the treatment of eosinophilic cystitis: a report of two cases

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**Palabras clave:** Síndrome hipereosinofílico. Cistitis eosinofílica. Mepolizumab.

### **Clinical Implications**

The first report of two patients with idiopathic eosinophilic cystitis successfully treated with mepolizumab.

Eosinophilic cystitis (EC) is a rare manifestation in the spectrum of hypereosinophilic syndrome (HES), characterized by eosinophilic infiltration of the bladder wall [1]. Its incidence is unknown and only few cases have been reported. A literature review of 135 patients in 2000, including secondary and idiopathic EC, reported urinary frequency, dysuria, pelvic pain and hematuria as the most frequent symptoms [2]. Peripheral eosinophilia was present in 43% and positive urine culture in 23%. The most common causes of EC include iatrogenic, neoplastic, infectious or post surgery etiologies but it can be idiopathic. The treatment is not standardized and in some cases, cystectomy may be necessary to improve the patient's quality of life.

Mepolizumab is a fully humanized monoclonal antibody that targets human IL-5, thereby blocking the binding of human IL-5 to the IL-5 receptor complex on the surface of eosinophil cell. By inhibiting IL-5, mepolizumab reduces the production and survival of eosinophils and suppresses eosinophil-driven inflammation. It is approved in Europe for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, severe chronic rhinosinusitis with nasal polyps and HES.

In case 1, a 69-year-old man was referred to Internal Medicine department by his urologist after being diagnosed with EC. He had been experiencing episodic hematuria, dysuria, and urinary frequency for the past 3 years. The patient had a history of ulcerative colitis that was surgically treated 20 years ago (without any ongoing treatment), and idiopathic chronic inflammatory demyelinating polyneuropathy that was treated with IV immunoglobulin five years ago.

During the three years preceding the diagnosis of EC, the patient underwent two transurethral resections of the prostate, several imaging procedures (ultrasound, CT scan, MRI), and two cystoscopies, without significant findings upon biopsy. He had received multiple courses of antibiotics and approximately five 2-week courses of corticosteroids per year. Although

corticosteroids provided temporary relief, he consistently experienced relapses, significantly impacting his quality of life.

The diagnosis of EC was confirmed based on significant circumferential thickening of the bladder wall with infiltration of adjacent structures (Figure 1A) observed on CT scan, as well as a bladder biopsy revealing a substantial eosinophilic infiltrate (Figure 1D, E) with up to 200 eosinophils per high-power field (HPF) and no presence of other inflammatory cells. Additionally, there was extension of the inflammatory lesions rich in eosinophils in the prostate tissue samples. Parasitic, neoplastic, and drug-induced causes of EC were ruled out. Laboratory investigations showed eosinophilia ( $0.66 \times 10^9/L$ ) and an elevated total IgE level (1500 kU/L). Serum levels of vitamin B12, tryptase, and C-reactive protein were within normal range. Analysis of lymphocyte phenotype revealed a T-LGL population CD8<sup>+</sup> CD57<sup>+</sup> accounting for 6% of total leukocytes, without evidence of clonal TCR rearrangement, which was considered unrelated to HES. Urinary cytology found 90 eosinophils per 100 cells.

To avoid repeated courses of corticosteroids, the patient was initiated on subcutaneous mepolizumab 100 mg per month following a 10-day course of corticosteroids. The patient was informed that this treatment was being used off-label. Three months after starting mepolizumab, significant improvement of the symptoms was observed, with no more hematuria or dysuria, and reduced urinary frequency. Urinary cytology revealed 55 eosinophils per 100 cells, and the eosinophil count was  $0.09 \times 10^9/L$ . The CT scan also showed improvement, with only persistence of infiltration in the anterior bladder wall (Figure 1B). One year after initiating mepolizumab, the patient remained symptom-free and was no longer taking corticosteroids. A CT scan showed a normal bladder (Figure 1C). However, urinary cytology still detected 31 eosinophils per 100 cells. Given the significant improvement in symptoms and CT scan results, no further biopsy was performed.

In case 2, a 14-year-old boy presented with abdominal pain and HE at  $7.3 \times 10^9/L$ . Abdominal ultrasound revealed ileal thickening, leading to the diagnosis of idiopathic eosinophilic enteritis. He was initially treated with a short course of corticosteroids, which resulted in significant improvement. However, one year later, he experienced a relapse with abdominal pain, pollakiuria, and dysuria. Gastric biopsies confirmed the diagnosis of eosinophilic gastroenteritis (EGE) (30 eosinophils per HPF in the small intestine), and a bladder biopsy showed a significant presence of eosinophils (180 eosinophils per HPF) in the chorion along with intravascular eosinophilia. Total IgE levels were elevated (1800 kU/L), while other biological assessments were normal. Corticosteroid treatment was resumed, but the patient relapsed again after two years, experiencing both digestive and bladder symptoms, with eosinophils reaching  $3.0 \times 10^9/L$  while on a prednisone dosage of 10mg/day.

The patient was enrolled in a trial involving intravenous mepolizumab administration at a dosage of 750mg per month, followed by subcutaneous injections of 300mg and 100mg per month. After initiating mepolizumab, the CT scan at 3 months showed a normal bladder and the patient remained free of relapses for 15 years.

## Discussion

The two cases presented here demonstrate different aspects of EC. The first had a single organ-restricted eosinophilic inflammation without HE. On the other hand, in the second case a multi-organ involvement was documented (EC and EGE) accompanied by severe HE. However, both cases can be classified as idiopathic HES [1] because there was no underlying cause of HE, no evidence of a reactive or neoplastic condition underlying HE; and because organ damage can be attributable to HE [1]. This classification is consistent with previous reports in the literature, as EC has not been commonly reported in cases of lymphoid HES [3,5] or clonal HES [5].

To the best of our knowledge, we present the first cases demonstrating the efficacy of mepolizumab in treating idiopathic EC. Given the clinical challenge of finding targeted therapies for EC to avoid the use of corticosteroids or invasive surgical procedures, the effectiveness of mepolizumab offers promise. Previous studies have reported the successful use of mepolizumab in treating other organ-specific HES, such as eosinophilic chronic pneumonia and EGE [6,7].

Three cases of EC successfully treated with another biologic, benralizumab (anti IL5-receptor) have been reported [8,10]. Among these cases, one was not apparently idiopathic as the patient had a history of renal cell carcinoma treated with nephrectomy, while the others were idiopathic. None of the patients exhibited blood HE or suffered from organ damage resulting from tissue HE. One patient required the insertion of bilateral nephrostomies, and all three showed resistance to oral corticosteroids.

These two cases suggest that mepolizumab may also be effective in the treatment of EC. This finding encourages further studies on the potential efficacy of mepolizumab in this specific patient population.

The patients gave their written consent to publication.

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## Conflicts of Interest

J.-E. Kahn reports consulting fees for advisory boards from AstraZeneca and GSK, research funding from AstraZeneca and GSK, and participation in clinical trials sponsored by AstraZeneca.

The remaining authors declare no conflict of interest.

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Figure 1. CT scan images of the first patient: prior to initiating mepolizumab treatment (A), at 3 months (B), and at one year (C). Urothelial lining with an eosinophilic infiltration of the chorion (hematoxylin eosin saffron (HES) x 200 (D), HES 400 (E)).

