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Title page.

Title: Mesalazine-induced eosinophilic glossitis and hypereosinophilia in a patient with ulcerative colitis: a case report and review of literature

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Main text.

A 74-year-old male, with a four-year history of ulcerative colitis (UC) treated with mesalazine, presented with episodic cheek and progressive tongue swelling respectively since 27 months. History revealed nocturnal sweating, difficulties swallowing solid food, loss of appetite and weight. There was no fever or atopy.

Physical examination showed an irregular heart rate and a symmetrically enlarged tongue with infiltrated edges (Fig. 1).

Blood analysis revealed leukocytosis $17.300 \times 10^3/\text{mm}^3$ (normal range $3.600\text{--}9.600 \times 10^3/\text{mm}^3$), with significant eosinophilia of $9.134 \times 10^3/\text{mm}^3$ (normal range $0.0\text{--}0.300 \times 10^3/\text{mm}^3$). Renal and liver function tests, C-reactive protein and urine analysis were normal.

Tongue and lip biopsy showed a dense eosinophilic infiltrate, extending into muscle and fatty tissue (Fig. 2). Chest-CT and PET-CT were normal. Cardiac MRI showed focal myocardial fibrosis.

Anti-myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibodies (ANCA) were positive (titer: 60 IU/mL). Antinuclear antibodies (ANA) were positive (titer: 1:2560, non-specific). C3/C4 complement levels were low (0.68 g/L and 0.06 g/L respectively).

A comprehensive work-up excluded major causes of eosinophilia: parasite infestations (negative stool ova and parasites test, including antigen for *G. lamblia*, *E. histolytica*/*E. dispar*, *C. parvum*), hypereosinophilic syndrome and eosinophilic leukemia (normal bone marrow aspirate and blood smear; negative FIP1L1/PDGFR α -associated fusion-gene), mastocytosis (normal serum tryptase).

Mesalazine hypersensitivity was suspected, but systemic corticoids did not improve symptoms. However, after mesalazine withdrawal, eosinophilia dropped significantly, tongue size normalized and appetite and weight increase recovered.

Patch tests with mesalazine 10% in water and petrolatum were negative. One year after stopping mesalazine the patient had no recurrence of UC, eosinophilia or tongue swelling.

Mesalazine is used to treat moderate UC and is generally well tolerated, but hypersensitivity reactions have been reported.

Common adverse effects include nasopharyngitis, nausea, headache, diarrhea, pyrexia, upper respiratory tract infections, sinusitis¹. Incidence of mesalazine-induced skin rash is 0.5-8.1%. Rare, but severe adverse events are pancreatitis and interstitial nephritis (incidence 0.3-1.8% and 0-1% respectively). Pneumonitis and pericarditis were reported anecdotally.

Mild peripheral eosinophilia not exceeding $0.8 \times 10^3/\text{mm}^3$ is described in UC³.

In our patient, eosinophilia occurred three years after starting mesalazine. Comprehensive work-up excluded other causes. We concluded that eosinophilic glossitis and peripheral eosinophilia were induced by mesalazine, because our patient's symptoms waned after stopping mesalazine and there was no flare-up within the following year.

This is the first case-report of mesalazine-induced eosinophilic glossitis with peripheral hypereosinophilia, which does not fulfill the criteria of DRESS syndrome⁴. Furthermore, isolated eosinophilic glossitis has not yet been reported as a drug-induced side effect.

Our patient tested positive for ANA and p-ANCA. Mesalazine has been associated with the ANCA and ANA-positivity. However, patients with UC can have positive p-ANCA⁵ (prevalence 40% - 88%)⁶. c-ANCA are associated with pulmonary vasculitis. Our patient had no signs of vasculitis, but vasculitis cannot be excluded due to low complement levels. After stopping mesalazine, ANCA remained positive and we assume their association with UC. Complement values returned to normal. Prevalence of ANA is 43% in UC⁷. In our patient, there were no signs of systemic lupus erythematosus or other systemic diseases.

Positive patch tests with mesalazine have been reported in 2 cases with skin symptoms^{8,9}, but not in mesalazine hypersensitivity without skin symptoms¹⁰. Mesalazine-induced photosensitivity has been described in several cases^{11,12}, particularly phototoxicity, which can be confirmed by photo-provocation tests with a minimal erythematous dose (MED) response below normal values in the UVA range.

In our patient skin patch testing with mesalazine was negative, but the complete resolution without subsequent flares strongly point towards a mesalazine-induced glossitis in our patient.

We report the first drug-induced eosinophilic glossitis with peripheral hypereosinophilia. Differential diagnosis for causes of eosinophilia is extensive and should always be thoroughly investigated.

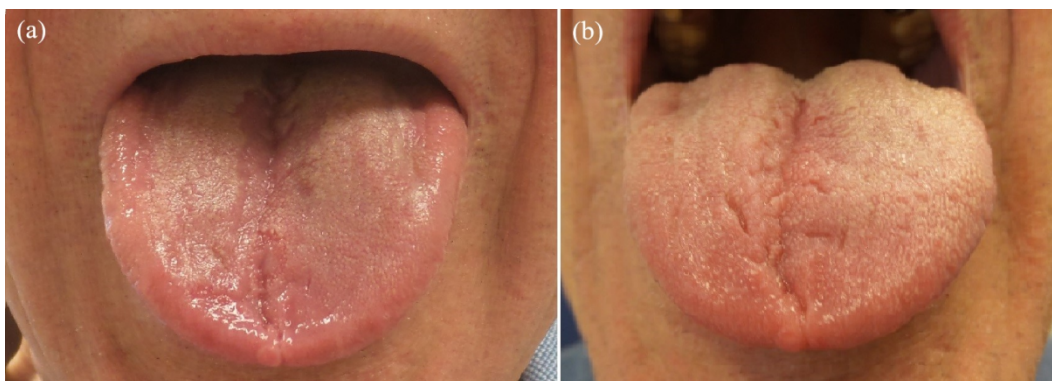
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The patient in this manuscript has given written informed consent to publication of their case details.

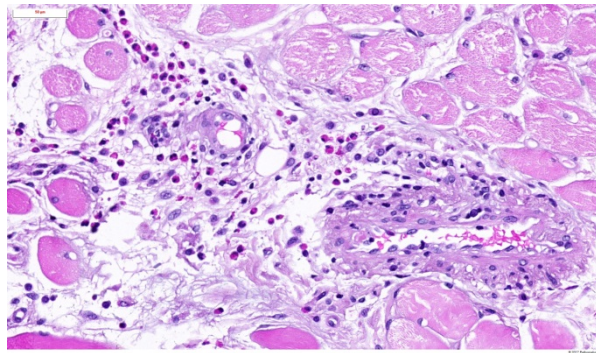
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