

Clinical Communications

Eosinophil-mast cell interaction: Mepolizumab leads to a reduction of clinical symptoms and serum tryptase in a patient with eosinophilic asthma and idiopathic mast cell activation

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Clinical Implications

- The administration of mepolizumab (monoclonal IL-5 antibody) in a patient with eosinophilic asthma and idiopathic mast cell activation syndrome led to an astonishing reduction in symptoms along with decreased serum tryptase levels. This finding suggests a possible eosinophil and mast cell interaction leading to changes in mast cell activation and degranulation.

Eosinophils and mast cells are originating from the same progenitor cells, effects of mast cells on eosinophils via IL-5 have been described, and interactions are known.¹ However, the effects of eosinophils on mast cells and newer eosinophil-targeting drugs are still poorly investigated. We hereby describe a case of a patient treated with the anti-IL-5 antibody mepolizumab for severe eosinophil-rich asthma and highly elevated serum tryptase and symptoms compatible to a high degree with idiopathic mast cell activation syndrome (iMCAS). Mepolizumab is a well-established treatment for eosinophilic asthma.² Treatment of eosinophilic asthma with the anti-IL-5 antagonist mepolizumab led to a substantial reduction in the iMCAS-associated symptoms and serum tryptase, suggesting a relevant impact of this drug on mast cells directly or by targeting eosinophils.

Mast cell activation syndrome is a type of mast cell activation disorder caused by mast cell mediator release. Symptoms can involve the skin as well as gastrointestinal, cardiovascular, respiratory, and neurologic systems.³ In mast cell activation syndrome, clonal mast cell proliferation as well as secondary activation of mast cells need to be ruled out.³

Our 42-year-old female patient initially presented with severe itch, chronic intermittent urticaria, headache, gastrointestinal troubles (diarrhea, cramps), episodes of tachycardia, general asthenia, and dyspnea during physical activity and intermittently when resting. She had no allergic symptoms and no constitutional symptoms.

A bronchial asthma had been diagnosed 10 years earlier and was treated with inhaled corticosteroids and beta-sympathomimetics as needed. Clinical examination was normal except for a positive dermographism. Laboratory testing showed elevated tryptase levels over 20 µg/L and an elevated blood eosinophil count. Serum chemistry values showed no signs of kidney or liver disease. Allergy testing results including skin prick tests with common inhalant and food allergens, specific IgE to food and inhalant mixes (fx5, sx1), and hymenoptera (honey bee,

wasp) done by ImmunoCAP and ImmunoCAP ISAC multi-screening were negative. Total IgE levels varied between 48.4 kU/L and 381 kU/L. A bone marrow biopsy and aspirate ruled out mastocytosis and myeloproliferative disease. C-KIT D816V mutational analysis in peripheral blood and bone marrow biopsy was negative (repeatedly in blood). Fluorescence in situ hybridization analysis was negative for PDGFRA/B- and FGFR1 as well as FIP1L1-PDGFRA excluding primary hypereosinophilic syndromes.⁴ Esophago-gastroscopy and colonoscopy did not show any signs of gastrointestinal eosinophilic disorders, and echocardiography showed normal cardiac function. Hereditary alpha tryptasemia was excluded by genetic analysis (Gene by Gene Test for the TPSAB1).⁵ The full workup done to rule out causes of primary and secondary eosinophilia as well as hyper-tryptasemia is summarized in Table I. Finally, diagnoses of idiopathic mast cell activation syndrome and eosinophilic bronchial asthma were made.

iMCAS symptoms responded partially to oral antihistamines (H1-blockers) (terfenadine 180 mg up to 3 times daily, bilastine 20 mg up to 4 times daily) but did not allow full control of symptoms. iMCAS-specific symptoms were assessed using a visual analogue scale (VAS)-based estimated symptom score⁶ of the patient including nausea, gastrointestinal troubles, diarrhea, headaches, and asthenia (VAS score maximum 9). Asthma symptoms did not respond sufficiently to inhaled corticosteroids and betamimetics, assessed by pulmonary function tests. Treatment with omalizumab (300 mg every 4 weeks) for 6 months was initiated, which led to partial reduction of urticarial and gastrointestinal symptoms (VAS score 6) as well as to a reduction in serum tryptase. The treatment however did not improve asthma control subjectively or in pulmonary function testing. Treatment with omalizumab was discontinued at the request of the patient and only oral antihistamines continued.

Because of marked eosinophilia and elevated eosinophilic cationic protein (ECP) levels, mepolizumab (100 mg subcutaneously) was administered every 4 weeks. Asthma symptoms, blood eosinophilia, and ECP were reduced 8 weeks after initiation of treatment with mepolizumab. In addition, a substantial reduction in serum tryptase levels and an improvement in iMCAS-specific symptoms summarized in a drop in VAS-based estimated symptom score (VAS score 2) were observed. During 2 probatory treatment pauses of mepolizumab, requested by the patient because of a satisfying reduction in symptoms, levels of serum tryptase and ECP rose and peripheral eosinophilia recurred (cycles 1-3). Treatment with mepolizumab was restarted twice and showed the same astonishing response, with a strong reduction in clinical symptoms as well as reduced serum tryptase, ECP, and eosinophil levels. Figure 1 summarizes the effect of mepolizumab on serum tryptase, eosinophil counts, and ECP over the course of 22 months. Figure E1 in this article's Online Repository at www.jaci-inpractice.org shows a comparable reduction in serum tryptase during treatment with omalizumab. This may partially be explained by the effect on FcεRI expression on mast cells.

To our knowledge, this is the first report of a beneficial response to mepolizumab in a patient with iMCAS or other mast

TABLE I. Diagnostic testing leading to diagnosis of iMCAS

Diagnostic testing	Result
Bone marrow biopsy	- Normocellular, normal hematopoiesis, no clonal proliferation of mast cells or atypical mast cells. FACS: No atypical mast cell or mast cell markers - FISH: FIP1L1-PDGFR α /CHIC2 Del., PDGFR α -B-, FGFR1 Rearrangement: negative - Kit Exon 17 Genotyping: no signs of mastocytosis, cKit D816V mutation negative
Colonoscopy, gastroscopy	No signs of eosinophilia or mast cell infiltration on esophageal, gastric, colon, and ileic biopsy specimens (CD117 stain)
Skin biopsy	Normal skin biopsy, no mast cell infiltrates (CD117 stain)
Parasite testing in serum, stool for ova and parasites	Negative
Allergy testing	Negative skin prick test results and serum specific IgE serologies to food and inhalant allergens (fx5, sx1) and hymenoptera venom (honey bee i1, wasp i3) by ImmunoCAP; ImmunoCAP ISAC multiscreening fully negative (112 molecular allergens)
Bone marrow density	No signs of osteopenia/osteoporosis
Genetic testing for familial alpha hypertryptasemia HAT	Negative gene by gene test result for TPSAB1 (no increased TPSAB1 copy number, calculated number of copies for alpha-tryptase and beta-tryptase is 2)
Lung function testing	Regularly done every 3-6 mo, ranging from FEV ₁ 67%/FENO 57 ppb (inhaled corticosteroids) to FEV ₁ 71.9%/FENO 38 ppb (omalizumab) and FEV ₁ 81%/FENO 17 ppb (mepolizumab)
Serum chemistry	Blood urea nitrogen, creatinine, liver function tests, electrolytes within normal limits
Resting ECG, echocardiography	Normal time indices and no signs of conduction disorder, normal cardiac function

ECG, Electrocardiogram; FACS, fluorescence-activated cell sorting; FENO, fractional exhaled nitric oxide; FISH, fluorescence in situ hybridization; HAT, hereditary alpha tryptasemia.

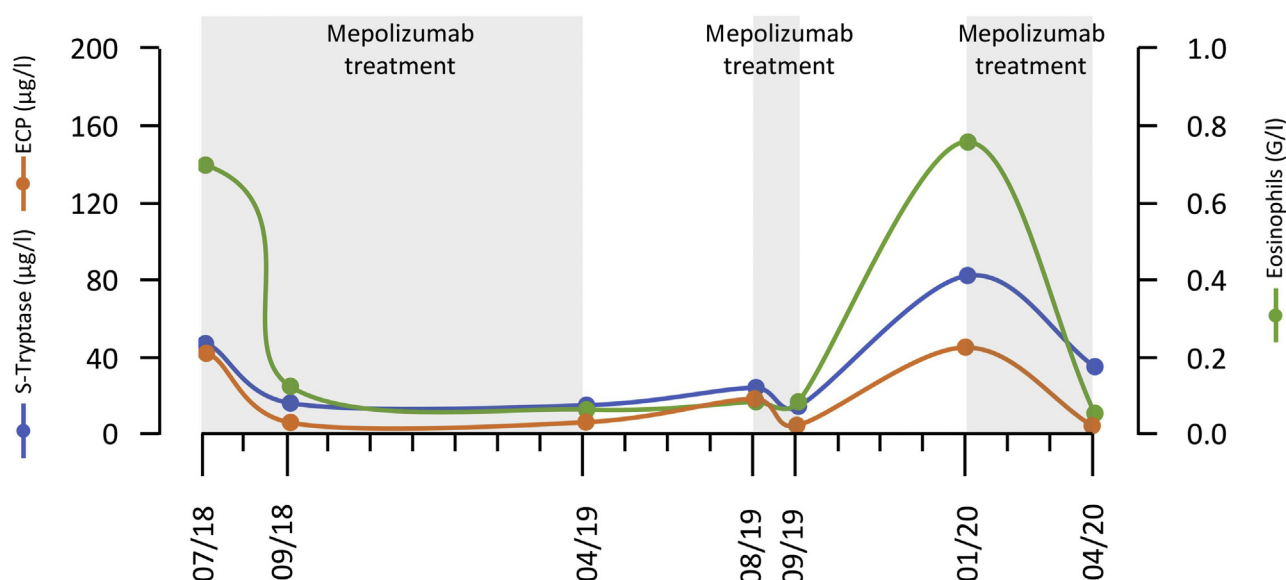


FIGURE 1. Effect of mepolizumab on serum tryptase, eosinophil counts, and ECP over the course of 22 months. Date (month/year) is given on x-axis, and concentration of respective laboratory parameter is given on y-axis. Time of mepolizumab application is shaded gray; dosage was 100 mg every 4 weeks.

cell-related disease. Treatment response was monitored by pulmonary function test, eosinophil count, ECP, serum tryptase levels, and clinically (VAS).

Our case points out an eosinophil-mast cell interaction, which has been described both in allergic and in mast cell diseases; possible factors are mast cell-eosinophil pairing⁷ and eosinophilic major basic protein leading to mast cell activation via integrin-beta 1.⁸ Also, eosinophils are able to establish physical contact with mast cells via their surface receptors (sialic acid-binding immunoglobulin-like lectins, Siglec-7 and 8), and may therefore also play a role in chronic spontaneous urticaria and treatment response as recently suggested by Kolkhir et al.⁹

Our findings underline the need for further studies on the role of IL-5 and eosinophils in mast cell diseases as well as the potential use of mepolizumab in the treatment of mast cell-related diseases.

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Figure E1 shows a mild reduction in serum tryptase levels during treatment with omalizumab. This may partially

be explained by the effect on FcεRI expression on mast cells. Additional laboratory parameters during and before treatment with omalizumab and mepolizumab can be found in Table E1.

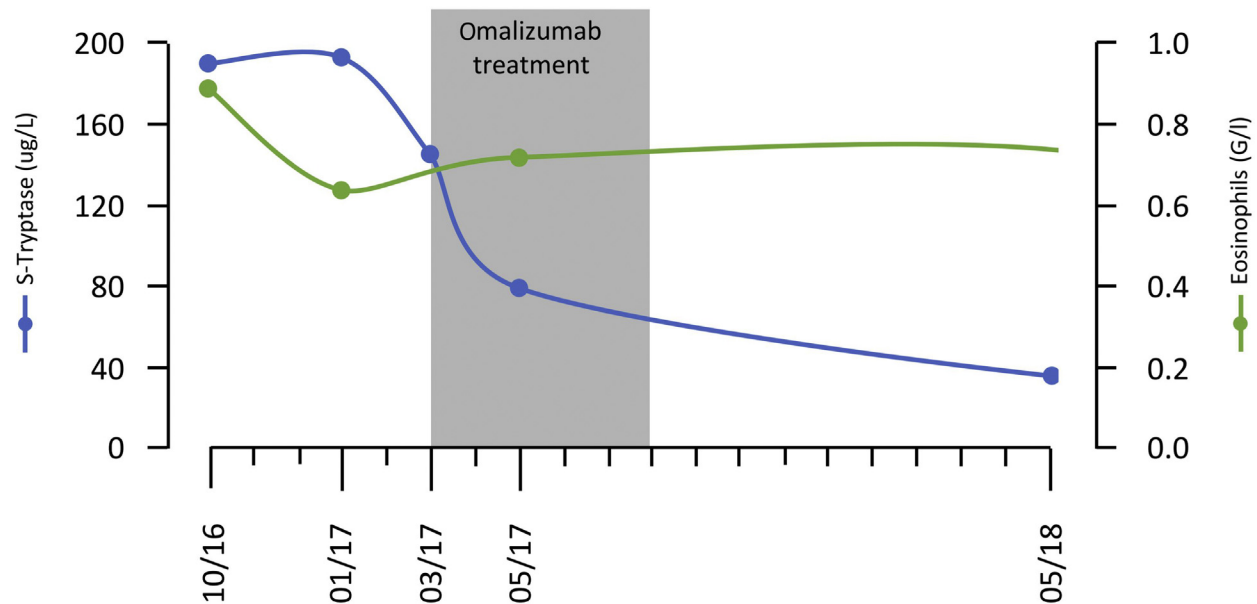


FIGURE E1. Effect of omalizumab on serum tryptase levels before treatment with mepolizumab. Date (month/year) is given on x-axis; concentration of respective laboratory parameter is given on y-axis. Time of omalizumab application is shaded gray; dosage was 300 mg every 4 weeks.

TABLE E1. Evolution of absolute eosinophil count, IgE, tryptase, and ECP

Date	Eosinophil count (<0.7 G/L)	Total IgE level (<100 kU/L)	Tryptase (<11.4 µg/L)	ECP (1.8-13.3 µg/L)	Treatment	Treatment of mast cell activation syndrome
07.10.15	0.13	65.5	72	NA	Inhalant	Antihistamines
18.2.16	1.13	NA	NA	NA	Inhalant	Antihistamines
15.3.16	1.37	NA	77.4	NA	Inhalant	Antihistamines
11.7.16	0.61	NA	NA	NA	Inhalant	Antihistamines
14.10.16	0.90	81.5	178	NA	Inhalant	Antihistamines
07.12.16	0.99	NA	193	NA	Inhalant	Antihistamines
22.03.17	0.22	381	146	NA	Omalizumab	Antihistamines and omalizumab
26.05.17	0.73	NA	81	NA	Omalizumab (stop in 08/17)	Antihistamines
26.04.18	0.71	NA	38	24.0	Inhalant	Antihistamines
24.05.18	0.73	NA	56.8	NA	Inhalant	Antihistamines
05.07.18	0.63	NA	49.3	36.9	Before start mepolizumab (cycle 1)	Antihistamines
31.08.2018*	0.06	NA	19.8	NA	Mepolizumab	Antihistamines and mepolizumab
16.11.18*	0.07	81.8	17.7	7.25	Mepolizumab	Antihistamines and mepolizumab
Discontinuation of mepolizumab from 04/2019 to 08/2019						
22.08.19†	0.1	73.7	26.9	17.40	Mepolizumab (cycle 2)	Antihistamines and mepolizumab
26.09.19†	0.1	73.4	17.3	6.04	Mepolizumab	Antihistamines
Discontinuation of mepolizumab from 09/2019 to 01/2020						
21.01.20‡	0.77	NA	84	39.5	Mepolizumab (cycle 3)	Antihistamines and mepolizumab
17.04.20‡	0.07	NA	37.6	5.88	Mepolizumab	Antihistamines and mepolizumab
17.08.20‡	0.09	78	36.4	NA	Mepolizumab	Antihistamines and mepolizumab

NA, Not available.

*Cycle 1 with mepolizumab.

†Cycle 2 with mepolizumab.

‡Cycle 3 with mepolizumab.