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Last station in the eosinophilic asthma with chronic rhinosinusitis and/or nasal polyposis march: Eosinophilic asthma with radiological findings associated with blood eosinophilia

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ABSTRACT

Objective: Eosinophilic asthma with chronic rhinosinusitis and/or nasal polyposis (EA-CRS/NP) is a subphenotype of adult-onset eosinophilic asthma. Blood eosinophil levels are shown to be highly elevated in patients with EA-CRS/NP and have potential for tissue infiltration. We aimed to demonstrate the clinical features of the patients who have a blood eosinophil level above 10% and have thorax computed tomography findings due to blood eosinophilia. **Methods:** Patients who were followed up in our clinic between 2012 and 2017 were retrospectively evaluated. Inclusion criteria were as follows: 1) Eosinophilic severe asthma, 2) eosinophilia >10%, 3) chronic sinusitis and/or nasal polyps, 4) patients with pathologic findings on thorax computed tomography, 5) regular follow-up for at least 1 year. **Results:** We identified 36 patients who met the above criteria. We defined this group as “Eosinophilic Asthma with chronic Rhinosinusitis and/or nasal polyposis with Radiological findings related to blood eosinophilia” (EARR). The mean age was 44.9 ± 11 years and 64% were females. Nasal polyps, aspirin exacerbated respiratory disease, and atopy, were present in 81%, 47%, and 25% of the patients, respectively. The mean blood eosinophil count was $1828.6 \text{ cells/mm}^3$ (19%). The majority of EARR patients had upper lobe dominant ground-glass opacities. The mean follow-up period was 3.2 ± 2.5 years. EARR patients did not evolve into eosinophilic granulomatous polyangiitis in the follow-up. **Conclusions:** This phenotype is the first eosinophilic asthma sub-phenotype reported in the literature. EARR is the final stage of the allergic march of EA-CRS/NP.

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Introduction

Adult-onset eosinophilic asthma is increasingly recognized as one of the most severe and difficult-to-treat asthma subtypes (1–3). Eosinophilic asthma with chronic rhinosinusitis and/or nasal polyposis (EA-CRS/NP) is a subphenotype of adult-onset eosinophilic asthma (4,5). The risk of eosinophilic asthma with nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity is higher in patients with eosinophilic nasal polyps. The risk of future aspirin-exacerbated respiratory disease (AERD) is also higher in patients with asthma and eosinophilic nasal polyps compared to other asthma patients without eosinophilic nasal polyps (6–8). Similar to relationship between atopic dermatitis, atopic rhinitis, and atopic asthma, there is also a “march” among this group of patients as CRS ► nasal polyps ► asthma ► AERD; however, it does not always have a certain order and may have variations (9).

Previous studies showed that $0.3 \times 10^9/\text{L}$ eosinophils in blood is the cut-off value to define eosinophilic asthma (10–13). More than $1500 \text{ cells}/\mu\text{L}$ is accepted as eosinophilia with the potential for tissue infiltration and is called hypereosinophilia (14). We noticed that in some patients with EA-CRS/NP, this potential pulmonary tissue infiltration could be demonstrated by radiological imaging. Thus, in this study, we tried to define and demonstrate the characteristics of this subset of EA-CRS/NP with a blood eosinophil level above 10% and thorax computed tomography (CT) findings that could be associated with eosinophilic tissue infiltration.

Method

Data of patients who were followed up with asthma in a university hospital between 2012 and 2017 were retrospectively evaluated. Those who had severe asthma and

CRS and/or NP and blood eosinophil count $>10\%$, and were regularly monitored for at least 1 year were selected. Among these, patients who had thorax CT for severe uncontrolled severe asthma were identified. Patients who had findings other than possible parenchymal or intraluminal eosinophilic infiltration, such as ground-glass opacities, centrilobular nodules, bronchial wall thickening, alveolar consolidation, and those who had systemic steroid treatment in the last 1 month were excluded from the study. Patients who had clinical signs and laboratory findings suggesting active pulmonary infection and other eosinophilic diseases with possible pulmonary infiltration were excluded. We defined this group as “Eosinophilic Asthma with chronic Rhinosinusitis and/or nasal polyposis with Radiological findings related to peripheral eosinophilia” (EARR), and clinical, laboratory and radiological findings, functional status, treatment history, and prognosis of this group were evaluated.

Definitions

Asthma: Asthma diagnosis was confirmed by a documented reversible airway obstruction [improvement in forced expiratory volume in one second (FEV_1) 12% of predicted and 200 mL after administration of 400 μ g salbutamol] (15). **Severe asthma:** Patients in which asthma is not under control despite Step 4 treatment or where a step decrease is not possible despite control with Step 4 treatment are classified as having severe asthma. The patients have definite asthma diagnosis who have no treatment or medication compliance problem and whose comorbidities have been treated (16). **Chronic rhinosinusitis:** All CRS subjects met the criteria for CRS as defined by the American Academy of Otolaryngology-Head and Neck Surgery Chronic Rhinosinusitis Task Force. The diagnosis of CRS was based on the presence of clinical symptoms (i.e., nasal congestion, rhinorrhea, facial pressure, hyposmia) persisting for more than 12 weeks in addition to objective evidence of chronic inflammatory disease on sinus CT imaging or nasal endoscopy. Sinonasal involvement was assessed by paranasal sinus computerized tomography (PNSCT) and nasal endoscopy (17). **Nasal polyp:** It is the polypoid inflammation filling the nasal airway in the PNCT. **NSAID hypersensitivity:** NSAID hypersensitivity was evaluated according to patients' clinical history compatible with COX-1 inhibitor intolerance. **AERD:** AERD was defined as the presence of CRS and/or NP, asthma, and NSAID sensitivity (18–20). Aspirin challenge tests were not performed to confirm the diagnosis of AERD. **Atopy:** Atopy was defined as skin-prick test positivity to at least one of the common aeroallergens. **Pulmonary function**

test (PFT) severity: PFT severity was classified into mild, moderate, or severe disease based on a percent-predicted FEV_1 of 80%–100%, 60%–79%, or less than 59%, respectively.

The following clinical, serological, functional, and radiological data obtained from medical records were reviewed and evaluated.

Patient characteristics: Sex, age, smoking history, presence of atopy, allergic rhinitis, CRS/NP, analgesic hypersensitivity, asthma, AERD, duration of asthma, duration of NP, hospitalization due to asthma in the preceding year, and admission to emergency room due to asthma in the preceding year.

Laboratory and functional tests: Blood eosinophilia: <300 cell/ mm^3 , C-reactive protein (CRP; reference range: 0–6 mg/L), erythrocyte sedimentation rate (ESR; reference range: 3–20 mm/h), total immunoglobulin E (IgE; reference range: 0–100 IU/mL), IgG, IgM, IgA, IgG4, *Aspergillus*-specific IgE, vitamin B12, antineutrophil cytoplasmic antibody (ANCA), and troponin. If suggested by hematology (FIP1-like-1-platelet-derived growth factor receptor alpha, JAK-2 mutation, Philadelphia chromosome), urinalysis, liver and renal function tests, parasite stool examination, hydatid IHA/IFAT, amoebiasis IFA, creatine kinase, anti-HIV, hepatitis markers, and PFTs [including FEV_1 , forced vital capacity (FVC), and FEV_1/FVC].

Imaging tests: Thorax CT, PNSCT, abdominal ultrasonography, echocardiography, and electromyography.

Evaluation of non-respiratory eosinophilic involvement

Cardiac involvement: The spectrum of cardiac manifestations of eosinophilic infiltration includes acute pericarditis, constrictive pericarditis, restrictive or dilated cardiomyopathy, myocarditis, and arrhythmias.

Renal involvement: Increased serum creatinine, proteinuria, or abnormal urinary sediment.

Gastrointestinal involvement: Unexplained abdominal pain, nausea, vomiting, diarrhea, and hemorrhage.

Peripheral neurological involvement: Newly developed mononeuropathy or multiple mononeuropathies.

Skin involvement: Active skin lesion (palpable purpura, subcutaneous skin nodules, urticarial rashes, cutaneous infarction, livedo reticularis).

Statistics

The data analysis was performed by SPSS statistical software (SPSS Inc. Chicago, Illinois) version 17. Central tendency and dispersion of numerical data were shown as mean $\pm$ standard deviation (SD). When comparing

Table 1. Characteristics of the patients at the time of diagnosis.

	N = 36
Female gender <i>n</i> (%)	23 (64)
Age, mean $\pm$ SD, years	44.9 $\pm$ 11
Smoking, <i>n</i> (%)	
Current smokers	1 (2.8)
Ex-smokers	3 (8.3)
Non smokers	28 (77.8)
Atopy, <i>n</i> (%)	9 (25)
Nasal polyps, <i>n</i> (%)	29 (80.6)
NSAIDs hypersensitivity, <i>n</i> (%)	17 (47.2)
Asthma duration before diagnosis [median, (min-max)], years	5.5 (1–30)
Nasal polyposis duration before diagnosis [median, (min-max)], years	8 (1–20)
Hospitalization in the last year, mean $\pm$ SD	0.6 $\pm$ 0.8
Emergency room admission due to asthma in the preceding year mean $\pm$ SD	2.1 $\pm$ 2.9
Use of SCS due to asthma in the preceding year mean $\pm$ SD	2.3 $\pm$ 1.8

Note. SD: standard deviation; NSAID: non-steroid anti-inflammatory drug; SCS: systemic corticosteroid.

continuous variables, an independent sample *t* test was used for parametric values. The *p* value of <0.05 was considered to be significant.

Results

Thirty-six patients were included in the study. The mean age was 44.9 $\pm$ 11 years and women represented 64% of the patients. Most of the patients (78%) did not have smoking history. CRS was present in all patients, and 81% and 47% of the patients had nasal polyps and AERD, respectively. Atopy was present in a quarter of the patients. NP had been diagnosed 8 years ago and asthma 5.5 years ago on average. The characteristics of the patients are summarized in Table 1.

The laboratory, PFT, and radiological findings of the patients are presented in Table 2. The mean eosinophil

Table 2. Laboratory, functional, and radiological data of patients at the time of diagnosis.

Parameters	Results
Blood eosinophil, mean $\pm$ SD, %	19 $\pm$ 9.9
Blood eosinophil, mean $\pm$ SD, cell/mm ³	1828.6 $\pm$ 1428.8
Total IgE, median (min-max), IU/mL	333.5 (9–1400)
ESR, mean $\pm$ SD, mm/h	11.4 $\pm$ 9.6
CRP, mean $\pm$ SD, mg/L	5.1 $\pm$ 3.2
ANCA positivity	None
Urine abnormality	None
FEV ₁ , mean $\pm$ SD, %	64.5 $\pm$ 18.2
Thorax CT, <i>n</i> (%)	36 (100)
Ground-glass opacities	24 (67)
Centrilobular nodules	8 (22)
Bronchial wall thickening	10 (28)
Alveolar consolidation	12 (33)

Note. SD: standard deviation; IgE: immunoglobulin E; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: antineutrophil cytoplasmic antibody; FEV₁: forced expiratory volume in the first second; CT: computed tomography.

Table 3. Comparison of clinical parameters before and after systemic corticosteroid treatment.

	Before treatment	After treatment	<i>p</i>
Emergency room visit	2.14 $\pm$ 2.9	0.14 $\pm$ 0.59	<0.001
Hospitalization	0.6 $\pm$ 0.8	0.08 $\pm$ 0.37	<0.001
Blood eosinophil, %	19 $\pm$ 9.9	3.9 $\pm$ 2.8	<0.001
FEV ₁ , %	64.5 $\pm$ 18.2	86 $\pm$ 13.8	<0.001

Note. Values given are the mean $\pm$ standard deviation.

SD: standard deviation; FEV₁: forced expiratory volume in the first second.

count at the time of diagnosis was >1500, which is the threshold for possible eosinophilic tissue infiltration. The FEV₁ values were low with a moderate obstructive pattern. ANCA positivity or urinary abnormalities were not present in any case. There was a dominance of ground-glass opacities on chest CT (Figure 1). The mean CRP and sedimentation values at the time of diagnosis were within normal limits. The patients were also evaluated for extrapulmonary involvement. None had any other system-specific symptoms; echocardiography and urinalysis did not show any pathology. Pruritus universalis was defined by only seven patients but no active skin lesion was detected, thus skin biopsy was not performed.

Methylprednisolone at 0.5 mg/kg/day for 2–4 weeks had been started in all patients due to worsening respiratory symptoms, tissue infiltrations that could not be explained by other pathologies other than eosinophilic tissue infiltration. Systemic steroid treatment was continued at the lowest dose that would maintain asthma control according to GINA Step 5 recommendations. Treatment with a mean maintenance dose of 4.7 $\pm$ 2.4 mg/day was continued for 1 year and it was possible to stop methylprednisolone in only three patients (8.3%). The mean follow-up duration was 3.2 $\pm$ 2.5 years. There was a significant decrease in the number of emergency room admissions and hospitalizations in the year following treatment. The eosinophil levels decreased and FEV₁ values increased significantly (Table 3).

Comparison of the laboratory, functional, and follow-up characteristics of the cases with and without AERD in this specific group showed no statistically significant difference (Table 4).

Table 4. Comparison of functional, laboratory, and follow-up data patients with and without AERD.

	AERD + N = 17	AERD – N = 19	<i>p</i>
Blood eosinophil, %	18.9 $\pm$ 11.4	19.1 $\pm$ 8.8	<i>p</i> > 0.05
Total IgE, IU/mL	225.7 $\pm$ 138.2	476.2 $\pm$ 431.8	<i>p</i> > 0.05
FEV ₁ , %	63.7 $\pm$ 16.32	65.17 $\pm$ 20.4	<i>p</i> > 0.05
Maintenance SCS dose, mg/day	4.05 $\pm$ 2.3	5.2 $\pm$ 2.5	<i>p</i> > 0.05

Note. Values given are the mean $\pm$ standard deviation.

AERD: aspirin-exacerbated respiratory disease; SCS: systemic corticosteroid; IgE: immunoglobulin E; FEV₁: forced expiratory volume in the first second.

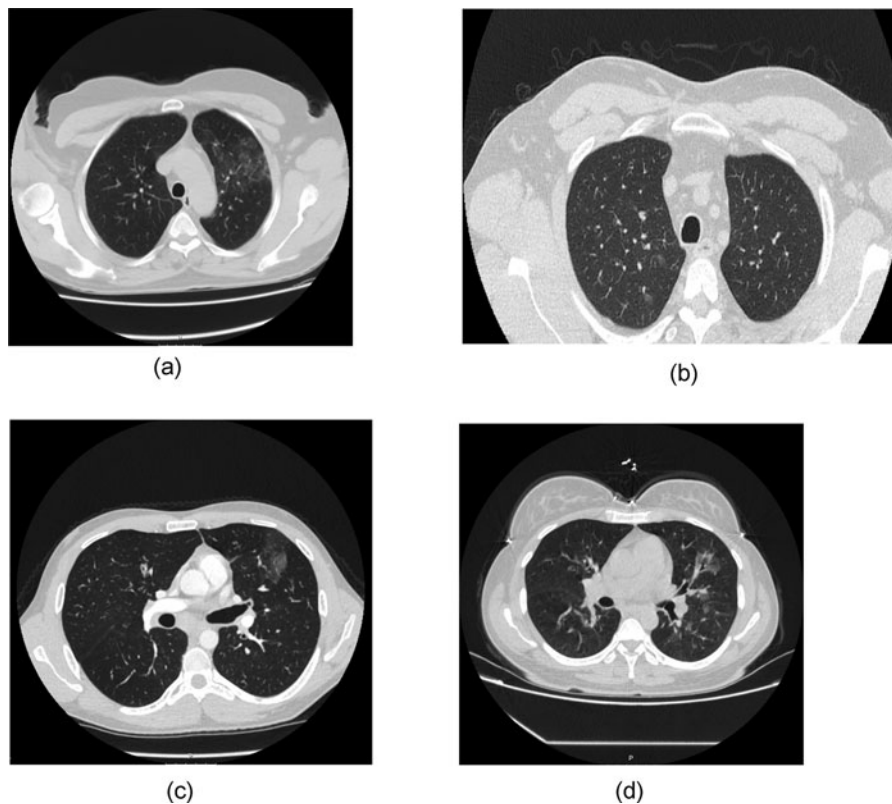


Figure 1. Ground-glass opacities with upper lobe predominance in the different EARR patients (a,b,c,d).

Discussion

In this study, we tried to define and demonstrate the characteristics of EARR. Patients with this phenotype show female predominance, low atopy rates, high blood eosinophil counts, high rate of AERD concurrence, and long-term systemic steroid dependence in order to keep the disease under control.

Asthma is no longer considered as a single disease, different phenotypes with potential underlying endotypes have been described over the last two decades (21–23). Adult-onset eosinophilic asthma is increasingly recognized as one of the most severe and difficult-to-treat asthma phenotype (1–3). This phenotype is associated with persistent airflow limitation (24) and risk of severe exacerbations (25). However, there is also a subgroup of adult onset eosinophilic asthma known as the EA-CRS/NP (4). This subphenotype seems to be in the initial stages of the EARR. The other point is that similar to atopic dermatitis, atopic rhinitis and atopic asthma, there is also an allergic march among this group of patients as CRS ► nasal polyps ► asthma ► AERD; however, it does not always have a certain order and may have variations (9). Our study showed that after AERD, the end stage of this eosinophilic march consists of eosinophilic pulmonary infiltrates depending on the severity of eosinophilic inflammation. The EARR is

the most severe clinical form of adult-onset eosinophilic asthma and is particularly seen in AERD and EA-CRS/NP patients. These patients had the most severe form because they all had very high eosinophil levels and radiological infiltrations associated with eosinophilia, they were all dependent on systemic corticosteroids and only a small percentage were able to discontinue corticosteroids. A blood eosinophilia level >1500 cells/mm³ can create the potential for tissue infiltration (14). All of our cases had severe eosinophilic asthma and the mean absolute eosinophil value was over 1500 cells/mm³, indicating that they had such potential. One of the hallmarks of chronic rhinosinusitis with nasal polyposis (CRSwNP) and AERD is an enhanced tissue eosinophilia compared to healthy sinonasal tissue (26). The unified airway hypothesis also suggests that disease in upper and lower airways is related. Patients with CRSwNP and asthma have significantly more severe radiological evidence of sinonasal inflammation and had undergone more sinus surgeries than patients with CRSwNP alone had (20). This is supported by a previous study in which CRS patients with asthma had more severe sinonasal inflammation and were more likely to have nasal polyps than CRS patients without asthma (27). In addition, another study found a significant positive association between the asthma severity and both the degree of sinonasal inflammation and

the likelihood of having nasal polyps (28). Thus, these observations led to the hypothesis that eosinophils are more highly activated in the new phenotype compared to CRSwNP or AERD. We could see the infiltration radiologically on thorax CT if the degree of sinonasal inflammation could be reflected in the radiological appearance (PNSCT) or even lead to nasal polyps by releasing their granule contents, and the increased eosinophils could lead to eosinophilic infiltration. However, this is only a hypothesis, as it was not confirmed by cytopathologic findings. Additional studies are needed to evaluate this hypothesis further.

In differential diagnosis, eosinophilic lung diseases which are a diverse group of pulmonary disorders associated with peripheral or tissue eosinophilia (Löffler's syndrome, chronic eosinophilic pneumonias, hyper-eosinophilic syndrome, allergic bronchopulmonary aspergillosis, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), malignancies (lymphoproliferative, myeloproliferative, and solid organ), and collagen vascular diseases) has been excluded in the study. Coincidental bacterial or viral pneumonia may occur in patients with asthma and eosinophilia. In our patients, pneumonia has been ruled out by means of the patients' clinical and laboratory findings, and corticosteroid response without antibiotics. However, the main problem is the differential diagnosis for the patients who meet the ACR classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA) but do not have an EGPA diagnosis, as there is no histopathological material. EGPA patients develop radiological signs secondary to vasculitis and eosinophilic infiltration of the respiratory tract. Likewise the asthma phenotype we defined, there are ground glass opacities with centrilobular nodules with upper lobe predominancy. The findings that differentiate this asthma phenotype from EGPA are; the lack of an elevated sedimentation rate, absence of extrapulmonary involvement, low atopy rates and most importantly, no symptoms or signs indicating vasculitis during the follow-up period. In addition, all cases showed a complete response to systemic corticosteroid treatment, and there was no need for the second-generation immunosuppressive treatments. We therefore believe that this specific group (EARR) can be considered as a phenotype of the eosinophilic severe asthma. The diagnostic terminology that could more closely define this group has been suggested by Cottin et al. as a revised nomenclature and definition for EGPA and a new proposed entity referred to as hypereosinophilic asthma with systemic (no vasculitis or ANCA positivity) manifestations (HASM) (29). However the study has been criticized by Lefèvre et al. (30) because the patients with HASM should not be considered as suffering from HES as indicated by the

2012 consensus expert workshop, and the 2015 update on WHO-defined eosinophilic disorders (31,32). It is also possible to assume this eosinophilic asthma phenotype that we defined overlapping with the EGPA eosinophilic phase localized to the respiratory tract (33).

In a study shown that patients with AERD have increased sinonasal inflammation on PNSCT, are more likely to undergo repeated sinus surgeries, and are more likely to have oral corticosteroid dependent disease than patients with CRSwNP and asthma. In addition, there was a trend toward significantly reduced lung function in patients with AERD versus patients with CRSwNP and asthma. The study suggests that patients with AERD have a different clinical profile than patients with CRSwNP and asthma (20). However, we did not find a difference between those with and without AERD in the group we defined. There was no difference between the severe EA-CRS/NP and the AERD subgroups for any of these parameters. The reason is that these were patients with final stage disease. Half of them had AERD while half had no COX sensitivity in addition to their severe eosinophilic asthma with rhinosinusitis/nasal polyps and both groups had radiological findings. Whether COX sensitivity was present or not made no difference in this group.

AERD is regarded as one of the specific asthma phenotypes. When individual cases are more insightfully analyzed, however, this group no longer appears to be so homogenous, differing in terms of specific clinical and laboratory parameters. In a study, four classes (subphenotypes) within the AERD phenotype were identified (34). In class 3, in which female patients outnumbered male patients, this was expressed by the presence of bronchial obstruction in all patients, frequent health care use, lack of asthma control, and the requirement for high doses of inhaled corticosteroids, oral corticosteroids, or both in the majority of patients. This class actually included the highest proportion of patients with severe and moderate levels of asthma severity. The AERD patients in our patient group also seem to be class 3 AERD patients. However, these cases had entered our defined group by going one level upwards.

The main limitation of the present study was that we did not show with transbronchial biopsy whether the thoracic CT findings were related to eosinophilic infiltration in patients who were considered to have the EARR. Bronchoscopy could not be performed in these patients because they had uncontrolled severe asthma at the time of diagnosis. However, the fact that the blood eosinophil levels, asthma clinical picture, and radiological infiltrates recovered once corticosteroid treatment was started shows that the pulmonary infiltrates were associated with eosinophilia although biopsy could not be performed. Another limitation was that the AERD

diagnosis was only made with the history and the NSAID sensitivity should normally have been confirmed with an aspirin provocation test. Studies have revealed that aspirin provocation tests are negative in 14% of patients with a clinical picture consistent with AERD and that the tests are positive in 15% of patients with asthma and chronic sinusitis with nasal polyps although there is no relevant history (20,35). However, the fact that the drug allergy history of our patients was evaluated by immunology/allergy specialists and that most patients had a history of a reaction to at least two different groups of NSAID indicate the strength of the NSAID sensitivity.

In conclusion, we defined an asthma phenotype with predominant centrilobular nodules and ground glass appearance, together with CRS/nasal polyps, where the upper lobe shows dominant involvement and is accompanied by a thorax CT appearance, consistent with eosinophilic infiltration in this study. We believe this phenotype is the final stage of the allergic march of the eosinophilic severe asthma phenotype with CRS/nasal polyps. It is the eosinophilic asthma phenotype that is more severe than the severe asthma phenotypes with AERD and CRS/nasal polyps. It is steroid-dependent, has high eosinophil values, and atopy is less common. In our study also, it has been shown that this asthma phenotype did not evolve into eosinophilic granulomatous with polyangiitis.

Conflict of interests

The authors declare that they have no personal or professional conflicts of interest regarding any aspect of this manuscript.

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