

[CASE REPORT]

Renal Involvement as Rare Acute Tubulointerstitial Nephritis in a Patient with Eosinophilic Disorder Treated with Early Add-on Administration of Mepolizumab

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Abstract:

A 39-year-old man presented with peripheral eosinophilia, pulmonary eosinophilic infiltrate, and renal failure due to acute tubulointerstitial nephritis (TIN). He had experienced childhood asthma and was negative for anti-neutrophil cytoplasmic antibody (ANCA). He was tentatively diagnosed with ANCA-negative eosinophilic granulomatous polyangiitis (EGPA) or idiopathic hypereosinophilic syndrome (HES). Renal involvement of isolated TIN with eosinophil infiltration is rare in EGPA and HES and does not seem to have a good prognosis in the literature. However, his condition improved well with corticosteroids and mepolizumab. The revised classification of EGPA based on the etiology should dictate the proper treatment in suspected EGPA patients with nonsystemic vasculitis.

Key words: anti-neutrophil cytoplasmic antibody, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, mepolizumab, tubulointerstitial nephritis

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Introduction

The diagnosis of idiopathic hypereosinophilic syndrome (HES) is based on Chusid's criteria, which are as follows: marked eosinophilia (absolute eosinophil count >1,500/ μ L), chronic course (>6 months), the exclusion of other evident etiologies for eosinophilia and signs or symptoms of eosinophil-mediated tissue injury (1). However, idiopathic HES and eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome (CSS), have a shared feature regarding the clinical phenotypes of hypereosinophilia and organ injuries. EGPA is a member of the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis family, although ANCA positivity is found in 30% to 40% of EGPA patients (2). The diagnosis of EGPA is usually easy when the patient has ANCA positivity with

typical clinical features and/or histological signs of vasculitis (3). However, in patients with a history of asthma and sinusitis, distinguishing between ANCA-negative EGPA and idiopathic HES is difficult due to the significant overlap in the clinical presentation and biomarker profiles (4).

We herein report an ANCA-negative patient with peripheral eosinophilia, pulmonary eosinophilic infiltrate and isolated tubulointerstitial nephritis (TIN) for which corticosteroid and mepolizumab were effective. The patient was tentatively diagnosed with idiopathic HES or ANCA-negative EGPA. Renal involvement as isolated TIN with eosinophil infiltration is rare in eosinophilic disorders. We performed a review of the literature in acute renal insufficiency due to isolated TIN in EGPA and idiopathic HES to examine their characteristics.

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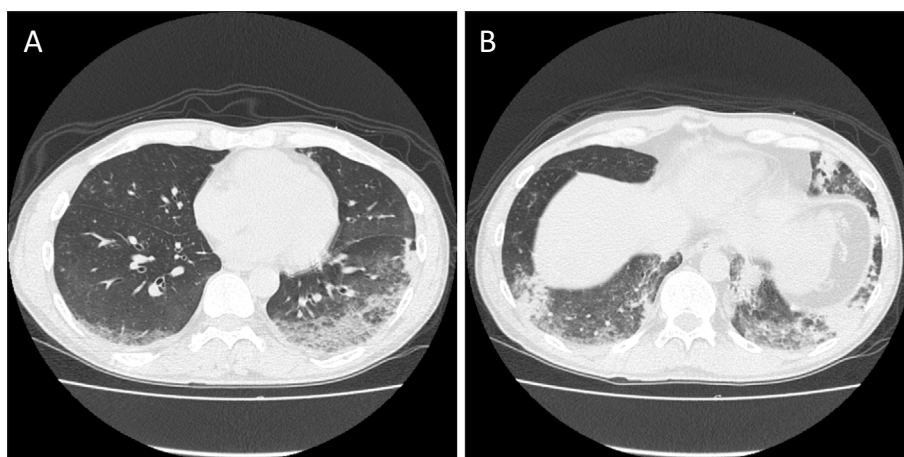


Figure 1. Plain CT of the chest A and B. Peripheral dominant multiple ground-glass opacities partly with consolidation in both lung fields are found.

Case Report

A 39-year-old man presented with headache and a fever 2 days prior to his admission and was treated with acetaminophen by a local physician 1 day prior. His symptoms worsened, and he appeared at the emergency unit in our hospital. He also complained of slight productive cough and mild diarrhea. Chest computed tomography (CT) revealed peripheral dominant multiple ground-glass opacities with consolidations in both lung fields (Fig. 1) and bilateral slight enlargement of the kidneys. He was admitted to our hospital with peripheral hypereosinophilia, pulmonary infiltrate and renal insufficiency. His medical history included childhood asthma at 5 years of age and appendectomy at 11 years of age. His asthma had been almost inactive except for slight symptoms when he had a cold. He was a current smoker. He had no food or drug allergies and used no over-the-counter drugs, medical herbal supplements or dietary supplements, except for acetaminophen 1 day before admission. He had no history of parasitic diseases and did not customarily eat raw or undercooked meat.

A physical examination on admission revealed the following: body height, 171.5 cm; body weight, 66.8 kg; temperature, 41.0°C; blood pressure, 141/86 mmHg; heart rate, 102 beats/min; and oxygen saturation, 95%. He did not show cardiac murmur or abnormal breath sounds. He had no abnormal findings upon examination of the tonsils, skin, peripheral lymph nodes, joints and neuromuscular system. A urinalysis revealed the following results: 1+ occult blood; 2+ protein; 20-29 red blood cells/high-power field and the presence of granular and waxy casts. Urinary chemistry revealed the following findings: protein, 0.30 g/g creatinine; N-acetyl- β -D-glucosaminidase, 29.2 U/L; β 2-microglobulin, 3,042 μ g/L; and alpha 1-microglobulin, 80.0 mg/L, indicating tubulointerstitial injuries. A blood analysis revealed the following findings: hemoglobin, 14.4 g/dL; white blood cell (WBC) count, 15,400/ μ L with eosinophil count, 2,156/ μ L;

platelet count, 170,000/ μ L; albumin, 3.2 g/dL; blood urea nitrogen, 8.9 mg/dL; creatinine, 1.21 mg/dL; Na, 139 mEq/L and K, 3.3 mEq/L. The immunological findings were as follows: C-reactive protein, 12.85 mg/dL; IgG 609 mg/dL, IgA 153 mg/dL, IgM 62 mg/dL, IgE 1,803 IU/mL (normal <100); hepatitis B and C serology, normal; human immunodeficiency virus antibody test, negative; anti-nuclear antibody, negative; anti-DNA antibody, negative; myeloperoxidase (MPO)- and proteinase 3 (PR3)-ANCA, negative; and anti-glomerular basement membrane antibody, negative. His results for allergic tests were negative. A cellular analysis of the bronchoalveolar lavage fluid revealed 30% eosinophils, indicating pulmonary eosinophilic infiltrate. An examination of the stool for parasites was negative. His diarrhea disappeared before the treatment. His electrocardiogram showed nonspecific T wave abnormalities. An echocardiographic examination detected a normal left ventricular function and no pericardial effusion or thrombus.

Steroid pulse therapy for 3 days with subsequent oral prednisolone at 50 mg/day was started for pulmonary eosinophilic infiltrate, and a deteriorated renal function with 6.04 mg/dL serum creatinine was noted on the 4th day after admission. Hemodialysis was introduced due to oliguria on the 5th day. Since the urinary volume was increased and the renal function began to improve, hemodialysis was not further required.

A kidney biopsy performed 8 days after the treatment revealed no glomerular lesions, including crescent formation, among 39 obtained glomeruli. There were many focal inflammatory cell infiltrations with a mild degree of tubulitis but no granulomas or peritubular capillaritis with neutrophil infiltration (Fig. 2A). Some inflammatory cell infiltrations in the tubulointerstitial areas included a moderate number of eosinophils (Fig. 2B). Edema and fibrosis were found in approximately 20% of the cortical areas. No vasculitis was found in any level of the arteries. An immunofluorescence study was negative for IgG, IgA, IgM, C1q and C3. These findings confirmed isolated acute TIN and suggested a re-

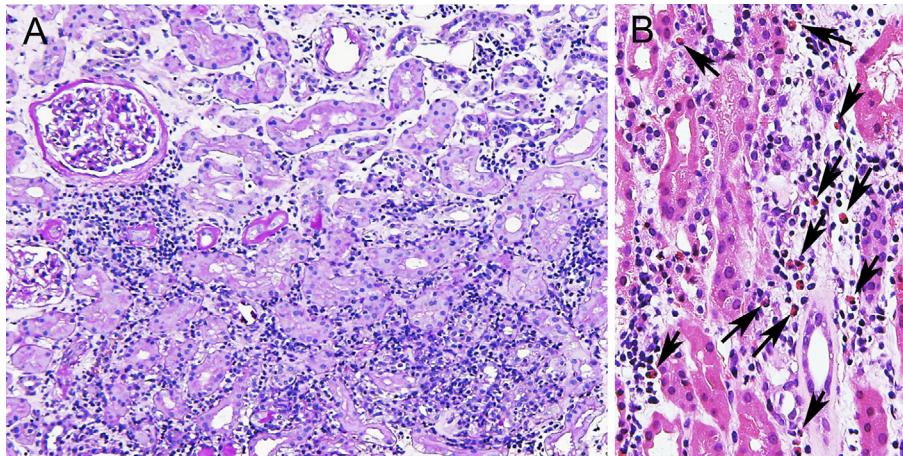


Figure 2. Light microscopic findings of a kidney biopsy. A: Focal interstitial inflammatory cell infiltrates are found. Periodic acid-Schiff staining. Original magnification $\times 200$. B: Interstitial inflammatory cell infiltrates with a moderate number of eosinophilic cells (arrows). Hematoxylin and Eosin staining. Original magnification $\times 400$.

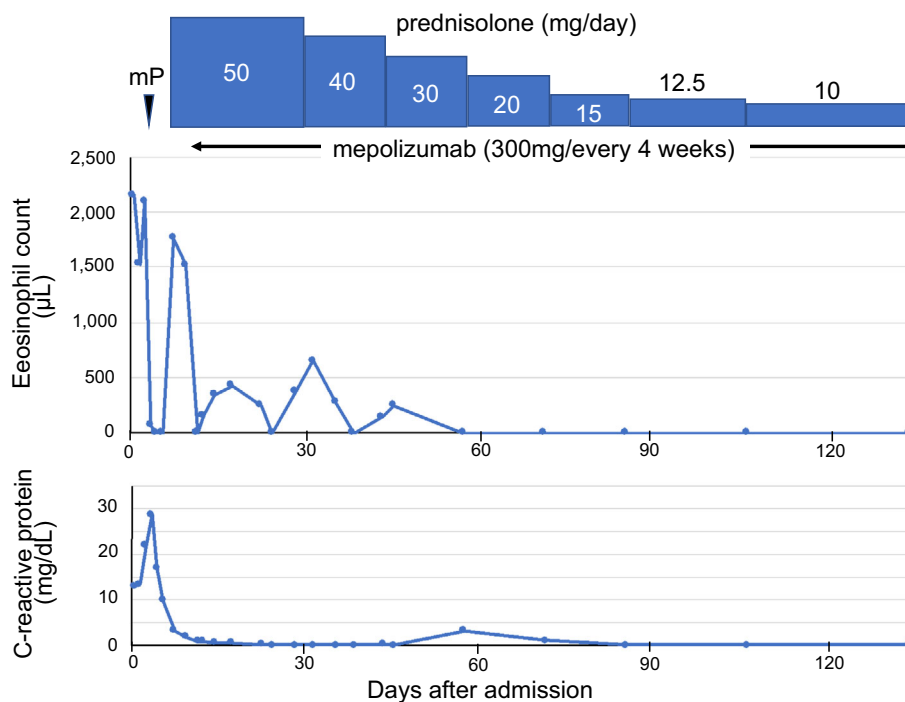


Figure 3. Clinical course. mP and arrowhead: steroid pulse therapy (1,000 mg methylprednisolone, daily boluses given for 3 days).

solving phase of eosinophilic TIN after corticosteroid therapy. Although isolated eosinophilic TIN is rare, he was tentatively diagnosed with suspected EGPA or idiopathic HES.

Just after steroid pulse therapy, his blood eosinophil count became $0/\mu\text{L}$ (Fig. 3). However, the percentage of eosinophils in the blood was more than 10% again, and 300 mg of the anti-interleukin-5 (IL-5) monoclonal antibody mepolizumab subcutaneously every 4 weeks was added to oral prednisolone at 50 mg/day 9 days after steroid pulse therapy to achieve remission, reduce the dose of prednisolone and prevent recurrence. His blood eosinophil proportion soon became 1% to 3% and was almost $0/\mu\text{L}$ at 2 months after the

treatment (Fig. 3). Urinary N-acetyl- β -D-glucosaminidase, β 2-microglobulin and alpha 1-microglobulin levels were normalized, and serum creatinine levels were decreased to 0.79 mg/dL 26 days after the treatment. Computed tomography revealed no ground-glass opacities or consolidations in either the lungs or the normal-sized kidneys at 24 days after the treatment. Prednisolone was reduced to 10 mg/day at 14 weeks after the treatment and tapered off. He remained well while receiving only mepolizumab at 300 mg every 4 weeks, and his blood eosinophil count was $114/\mu\text{L}$, IgE was 207 IU/mL, and serum creatinine was 0.80 mg/dL at 17 months after the treatment.

Discussion

We herein report an ANCA-negative patient with childhood asthma, peripheral eosinophilia, pulmonary eosinophilic infiltrate and acute renal insufficiency due to possible eosinophilic TIN who was successfully treated with corticosteroids and mepolizumab.

Our patient took a therapeutic dose of acetaminophen one day before admission. Acetaminophen-induced eosinophilic pneumonia has been reported in a small number of cases (5), and acute tubulointerstitial nephritis with eosinophil infiltrate due to acetaminophen was also reported in a few cases (6). However, no cases of drug-induced HES involving both the lung and kidney without dermatological involvement have been reported. Drug-induced HES may be caused by a delayed hypersensitivity reaction. When patients have previously been sensitized with acetaminophen, a delayed hypersensitivity reaction may occur soon after the repeated use of acetaminophen. However, it is unlikely that the severe lung and kidney involvement seen in our patient would have been induced only one day after acetaminophen use. Furthermore, the worsened renal function in our patient even after the discontinuation of acetaminophen did not support acetaminophen-induced HES.

EGPA is “Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia” (7). ANCA is more frequent when glomerulonephritis is present than in its absence (7). The diagnostic criteria for EGPA established by Lanham et al. include systemic vasculitis involving two or more extrapulmonary organs (8). Our patient did not show systemic vasculitic manifestations, so he did not meet Lanham’s criteria. A history of asthma is a key criterion for EGPA based on Lanham’s criteria (8) and the American College of Rheumatology 1990 criteria (3). Our patient had childhood asthma, but his asthma was not late- or new-onset or newly worsened, as is commonly seen in EGPA (9). Therefore, the diagnosis of EGPA was indeterminate in our patient.

In contrast, HES shares many features with EGPA. HES comprises a group of diseases that are characterized by prolonged peripheral eosinophilia and organ damage in the absence of secondary causes for eosinophilia. HES is classified as myeloproliferative, lymphoproliferative, overlap, idiopathic and associated variants of HES. Idiopathic HES is now restricted to patients with HES of undetermined etiology (1, 10). Although the chronic course of eosinophilia was not determined and precise examinations to classify HES were not performed in our patient, if he did not have EGPA, he seems to have had idiopathic HES.

According to a recent genome-wide association study with stratification by ANCA, EGPA comprises two genetically and clinically distinct syndromes (11). MPO-ANCA-positive EGPA is an eosinophilic autoimmune disease shar-

ing certain clinical features and an HLA-DQ association with ANCA-associated vasculitis, while ANCA-negative EGPA may instead have a mucosal/barrier dysfunction origin, sharing features with asthma (11). Interestingly, it has been suggested that patients who present with asthma, an eosinophil count above 1,500/ μ L and systemic manifestations (other than asthma, pulmonary or ear, nose and throat involvement) directly attributable to EGPA but no vasculitis or ANCA may be considered to suffer from idiopathic HES (12, 13). Even if the history of asthma in our patient is accepted as a criterion for EGPA, our patient might be considered to have had idiopathic HES.

Although ANCA-positive EGPA sometimes shows pauci-immune necrotizing glomerulonephritis with TIN with eosinophilic infiltration (7), patients with CSS/EGPA presenting with acute renal insufficiency due to biopsy-proven TIN in the English-language literature are rare. Recently, a multicentric retrospective study by the GERM“O”P and the European Respiratory Society Taskforce on EGPA reported no TIN in 157 EGPA patients based on the presence or absence of definitive vasculitis features and/or ANCA status (13). A more recent multicentric retrospective study of 63 biopsy-proven cases with EGPA (53 ANCA-positive cases and 10 ANCA-negative cases) revealed that isolated TIN was found in 5 (9%) ANCA-positive cases and 1 (10%) ANCA-negative case, suggesting that isolated TIN can occur in both ANCA-positive and ANCA-negative EGPA patients (14).

To our knowledge, renal insufficiency due to isolated TIN has been reported in only three CCS/EGPA cases, with some details included (15-17) (Table). In contrast, HES most commonly involves the heart, lungs, nervous system and skin (18). While renal involvement is rare in HES, renal manifestations include eosinophilic TIN, various types of glomerulopathies, thrombotic microangiopathy and electrolyte disturbances (18, 19). Three cases with isolated eosinophilic TIN in idiopathic HES (20-22) were found (Table). Based on the limited data of CSS/EGPA and idiopathic HES with isolated TIN (Table), the age of patients ranged from 25 to 77 years old. Most cases show pulmonary involvement, although whether or not pulmonary involvement is caused by eosinophil infiltration is unclear. High IgE levels were found in most cases. Urinary abnormalities tended to be mild, similar to those associated with other causes of TIN. Two of the patients required temporary dialysis therapy, but one had chronic kidney disease due to diabetic nephropathy. At least half of the cases had irreversible severe renal damage. The characteristics were compatible with those in our patient except for the poor renal prognosis. The mechanisms underlying eosinophilic TIN in eosinophilic disorders are suspected to involve eosinophil cytotoxicity and the mass effect due to eosinophilic infiltrates, which are also implicated in other damaged organs. However, the precise reason why isolated eosinophilic TIN has rarely been associated with eosinophilic disorders is unclear when compared with eosinophilic infiltration in other organs.

Table. Cases with Eosinophilic Granulomatous Polyangiitis/Churg-Strauss Syndrome and Idiopathic Hypereosinophilic Syndrome Presenting with Acute Renal Insufficiency Due to Isolated Tubulointerstitial Nephritis with Eosinophilic Infiltration.

Reference	15	16	17	20	21	22	Our case
Diagnosis	CSS	CSS	EGPA	iHES	iHES	iHES	EGPA/iHES
Age/Sex	37/M	77/F	25-35/F	55/M	40/M	73/M	39/M
History of eosinophilia	NR	2 years	NR	6 years	at least 6 months	NR	Unknown
Proteinuria	3+	0.35 g/day	0.1 g/day	3+, 7.2 g/day	0.77-0.49 g/gCr	Negative	2+, 0.3 g/gCr
Hematuria	3+	2+	NR	RBC 15/HPF	NR	Negative	1+, RBC 20-29/HPF
Eosinophils (μL)	9,997, 51.8%	1,500<	45%	5,984, 32%	35,000	4,953, 48%	2,156, 14%
Serum Cr (mg/dL)	11.52 (transient HD and PD, AKI on CKD due to diabetic nephropathy)	3.3	1.47	4.79	3.69	7.45 (transient HD)	6.04 (transient HD)
IgE	High	NR	Normal	High	High	High	High
ANCA	PR3	MPO	MPO	NR	NR	NR	Negative
Renal histology	Eosinophilic TIN with granuloma, Diabetic nephropathy	Eosinophilic TIN	TIN with eosinophilic infiltrates	Acute and chronic TIN with eosinophilic infiltrates	Eosinophilic TIN	Chronic eosinophilic TIN	Acute TIN with moderate eosinophilic infiltrates
Other organ involvements	Brain, lung, heart, liver, skin	NR	Nose, joint, lung, skin	Lung, heart	Lung, heart	Lung, heart	Lung
Vasculitis	Positive	NR	Positive	Negative	Negative	Negative	Negative
Treatment	Pred	Pred+AZA	Pred+CTX, AZA	Pred	Pred	Pred	Pred+mepolizumab
Follow-up	NR	4 years	83 months	2 years	NR	NR	15 months
Outcome, serum Cr (mg/dL)	5.09 (pre-AKI level)	2.1	0.56	2.99	NR	2.14	0.78

CSS: Churg-Strauss syndrome, EGPA: eosinophilic granulomatosis with polyangiitis, iHES: idiopathic hypereosinophilic syndrome, M: male, F: female, Cr: creatinine, RBC: red blood cell, HPF: high-power field, HD: hemodialysis, PD: peritoneal dialysis, AKI: acute kidney injury, CKD: chronic kidney disease, ANCA: anti-neutrophil cytoplasmic antibody, PR3: proteinase 3, MPO: myeloperoxidase, TIN: tubulointerstitial nephritis, Pred: prednisolone, CTX: cyclophosphamide, AZA: azathioprine, NR: not reported

The routine treatment strategy for EGPA and idiopathic HES relies mainly on corticosteroids with immunosuppressive therapy (23, 24). Immunosuppressive agents are used for the induction and maintenance of remission in patients with relapsing or refractory EGPA and HES despite limited efficacy. The renal prognosis in CSS/EGPA and idiopathic HES patients with isolated eosinophilic TIN does not seem to be good among the small number of reported cases (Table). At least half of the patients had severe renal dysfunction. However, they received only corticosteroids, and two patients were also treated with immunosuppressants. Recently, biologics, including mepolizumab, a humanized monoclonal antibody against IL-5 that reduces blood eosinophil counts, have been used to treat severe asthma and eosinophilic disorders, including EGPA and idiopathic HES (25). However, mepolizumab was effective in achieving protocol-defined remission in approximately half of EGPA patients but not in the entire trial cohort in MIRRA, a phase III trial (26). One potential reason for this is that EGPA is a heterogeneous disease with some manifestations being noneosinophil-driven (26). For HES, a randomized, placebo-controlled phase III study demonstrated that treatment with mepolizumab was effective in 72% of patients with HES and was associated with a 50% reduction in the proportion

of patients who experienced 1 or more flares during the 32-week treatment period compared with treatment with placebo (27).

Our patient with EGPA or idiopathic HES had severe pulmonary involvement and severe renal involvement requiring hemodialysis and started off with high-dose corticosteroids treatment. His blood eosinophil count became 0/ μL just after steroid pulse therapy (Fig. 3). However, the percentage of eosinophils in the blood increased to over 10% again while on prednisolone at 50 mg/day. Therefore, we considered reinforcement of the treatment to induce early remission and prevent irreversible damage to the lung and kidney. Immunosuppressive agents, including intravenous cyclophosphamide, showed limited efficacy and induced marked adverse effects. Intravenous immunoglobulin therapy is effective against residual peripheral neuropathy due to mononeuritis multiplex (28), but our patient was not indicated for it. Therefore, we decided to perform the early introduction of mepolizumab since we expected a rapid remission with a maintenance of such remission without any significant adverse effects. Our patient had a very good response to treatment with mepolizumab as an add-on therapy to corticosteroid treatment for EGPA (26, 27), probably because the disease was eosinophil-driven. The clinical benefits of treat-

ment with mepolizumab in our patient may include early recovery of symptoms and organ damage, prevention of recurrence and the ability to decrease the prednisolone dose at an early point. Proper and prompt treatment based on the etiology of eosinophilic disorders is necessary before irreversible organ damage occurs.

In summary, we presented an ANCA-negative, nonvasculitic case with childhood asthma, eosinophilia, pulmonary eosinophilic infiltrate and rare isolated TIN. Though our case was difficult to definitively diagnose with EGPA or idiopathic HES, he was successfully treated with corticosteroids and mepolizumab. Regarding the choice of treatment strategy, a revised classification of EGPA based on the etiology may be required, especially in ANCA-negative, nonsystemic vasculitic EGPA patients at the present classification.

The authors state that they have no Conflict of Interest (COI).

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