

A Patient with POEMS Syndrome: The Pathology of Glomerular Microangiopathy

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POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) is potentially fatal multisystem disorder but its renal complication has often been overlooked because renal involvement is not necessarily included in the diagnostic criteria of POEMS. This report documents the patient with POEMS syndrome with long-term renal histopathological changes evaluated by renal biopsy. A 32-year-old Japanese woman presented with symptoms consistent with POEMS syndrome associated with proteinuria and IgA- λ type monoclonal gammopathy. Initial renal biopsy for confirmation of diagnosis revealed the proliferation of glomerular capillary loops located in the expanded mesangial matrices associated with glomerular enlargement. Electron microscopy examination of the renal biopsy revealed the presence of double contoured glomerular basement membrane containing peculiar fibrillary structure. The patient was therefore initially diagnosed as membranoproliferative glomerulonephritis (MPGN)-like lesion without any significant immunoglobulins and complements deposition. The patient was subsequently admitted to hospital on five occasions due to renal dysfunction and anasarca for the next four years of her clinical course. The severity of anasarca was correlated mainly with serum titer of vascular endothelial growth factor (VEGF) during this period. Acute renal failure occurred at the last admission and the second biopsy was performed. An increased mesangial matrix and frequent global sclerosis of the glomeruli with arteriosclerosis was noted in this second biopsy compared to the first one. These findings of renal biopsies suggest that the glomerular microangiopathy of POEMS syndrome may occur in the context of systemic capillary leak syndrome superimposed on chronic endothelial injury.

Keywords: anasarca; electron microscopy; POEMS syndrome; renal biopsy; vascular endothelial growth factor
Tohoku J. Exp. Med., 2013 November, 231 (3), 229-234. © 2013 Tohoku University Medical Press

Introduction

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) is a relatively rare disorder defined by the presence of proliferation of plasma cells and multiple clinical symptoms such as polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. This rare syndrome has been reported to occur particular with high incidence in Asian countries, including Japan (Semble et al. 1986; Fukatsu et al. 1991, 1992; Mizuiri et al. 1991; Nakazawa et al. 1992; Hitoshi et al. 1994; Watanabe et al. 1996; Nakamoto et al. 1999; Sanada et al. 2006). This syndrome has also been known as a potentially fatal disease associated with a substantial deterioration in quality of life through neuropathy, anasarca, or thromboembolic events,

and/or cachexia (Nakanishi et al. 1984; Dispenzieri et al. 2003).

Renal functional impairment is not included in the diagnostic criteria of POEMS (Dispenzieri et al. 2003; Kuwabara et al. 2012) but renal involvement proceeds together with systemic symptom such as neuropathy and anasarca with occasional reported cases of acute renal failure (Fam et al. 1986; Sano et al. 1986; Nakamoto et al. 1999). A study examining the outcome of 52 Japanese POEMS patients with confirmed renal pathology over duration of 51.2 months showed that 54% of the patients had serum creatinine levels of more than 1.5 mg/dl and one fifth of the patients developed symptoms requiring dialysis (Nakamoto et al. 1999). Therefore, it is important to study the details of renal pathology of this disease but has not been studied in details. In this study, we report a case of

Received May 7, 2013; revised and accepted October 24, 2013. Published online November 16, 2013; doi: 10.1620/tjem.231.229.

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POEMS syndrome and evaluated its glomerular microangiopathy, in which the renal biopsy at the beginning and the end of the 4-year interval documented a progression in renal histopathology.

Clinical Course

A 32-year-old Japanese woman was admitted to the hospital because of a 5-month history of abdominal bloating and anasarca. She had a past history of endometriosis. On admission, the height and body weight of the patient was 166.5 cm and 60.8 kg, respectively. Her temperature was 36.5°C. Blood pressure was 128/88 mmHg. Physical examination revealed the chest rales at auscultation, facial edema, hemangioma-like verruca of the skin of the back, multiple lymphadenopathy and splenomegaly with amenorrhea. An intrinsic muscle insufficiency was clinically suspected by the presence of hollow foot and peripheral nerve injury was also suspected in the lower limbs based upon the study of nerve conduction velocity and electromyography.

Blood count revealed anemia (Hb 10.3 g/dL) and blood chemistry lower levels of serum total protein (5.2 g/dL) and albumin (3.1 g/dL), but liver and renal function as well as levels of electrolytes and glucose was within normal limits. Serum immunoelectrophoresis revealed a band of M-protein of IgA- λ type but osteosclerotic myeloma was not detected. Bone marrow puncture revealed the presence of 0.6% plasma cells. Serum IgG, IgA, IgM, C3 and C4 were 1,024 mg/dL, 559 mg/dL, 192 mg/dL, 50 mg/dL and 17 mg/dL, respectively. The patient exhibited 0.3 g/day proteinuria, but no microhaematuria was seen. Commercially available kits for enzyme-linked immunosorbent assay (ELISA) were used to detect interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) (R&D System, Minneapolis, MN, USA) (Shikama et al. 2001). Increased levels of serum cytokines were also detected including IL-1 β as 0.699 pg/mL (normal < 0.567 pg/mL), IL-6 as 8.9 pg/mL (normal < 4.62 pg/mL) and VEGF as 83.2 pg/mL (normal < 38.3 pg/mL), respectively. Based on these findings, the patient fulfilled the diagnostic criteria for POEMS syndrome, which was also confirmed by the first renal biopsy (described later in histopathological findings). Following administration of methyl-prednisolone, anasarca decreased and her performance status improved. After initial admission, the patient was followed for a period of 4 years. In this period the patient was admitted 5 times due to progression of anasarca and decreased renal function. During all admissions, the serum creatinine and blood urea nitrogen (BUN) together with body weight fluctuated after an administration of methyl-prednisolone (Fig. 1A). During the 3rd admission the severity of serum creatinine level turned out to be correlated clinically with serum level of VEGF, and these levels were decreased by the administration of methyl prednisolone (Fig. 1B). Before the final (5th) admission acute renal failure occurred after severe diarrhea and dehydration resulting in the need for the patient to undergo hemodialysis. Urinalysis then revealed excretion

of urinary protein (+/-) with mild hematuria (red blood cells 6-10/HPF) and NAG (110.7 U/L). A fractional excretion of sodium (FENa) was 0.11%, suggesting prerenal acute renal failure. Therefore, the second renal biopsy was performed at 8 days after the final day of hemodialysis treatment.

Histopathological findings of renal biopsies

Histopathological findings in the first renal biopsy demonstrated a proliferation of the glomerular capillary loops in the expanded mesangial matrix resulting in double contour of the glomerular basement membrane (GBM) and glomerular enlargement (300 μ m). The diagnosis was membranoproliferative glomerulonephritis (MPGN)-like lesion (Fig. 2A and B). There was no evidence of endocapillary hypercellularity. Further examination by electron microscopy revealed an expanded subendothelial space and mesangial matrix, with peculiar fibrillary electron dense materials (Fig. 2C). No foot process effacement was detected in the podocytes. Interstitial edema was present without any inflammatory cell infiltration. No immunoglobulins or complements were detected by immunofluorescence analysis. Immunohistochemical analysis by using CD34 antibody (QBEnd/10, Novocastra Laboratories, Newcastle, UK) revealed abundant numbers of CD34-positive endocapillaries in the expanded mesangial lesion including within immature capillary formation (Fig. 3A). As a consequence, an increased number of capillaries insides expanded mesangial matrix resulting in reduced diameter of the capillary lumen, which were surrounded by a mixture of mature and immature endothelia was transformed from normal structure of the glomerulus (Fig. 3B).

The second biopsy demonstrated a progression of mesangial expansion together with an increase of PAM-positive matrix substance (Fig. 2D). Global and segmental sclerosis together with narrowing of the glomerular capillaries became more frequent (Fig. 2E). Electron microscopic examination revealed that in addition to the remaining fibrillary electron dense materials, mesangial interposition and dense substance became prominent in the mesangial matrix. Immature endothelial cells were detected around the narrow capillary lumens (Fig. 2F). Foci of marked intimal hyalinosis were also detected in afferent arteries. Arteriopathy with fibrous endoarteritis was not found in the interlobular arteries. Acute tubular necrosis was not apparent. In the tubulointerstitium various histopathological changes were apparent including 30% of total area being occupied with interstitial fibrosis and 20% of the total area showing lymphocyte infiltration.

Discussion

Our present case demonstrated the histological progression of POEMS in the kidney through an initial biopsy at diagnosis and subsequent biopsy 4 years after diagnosis. The glomerulopathy of POEMS syndrome has been reported by several terms such as MPGN-like lesion,

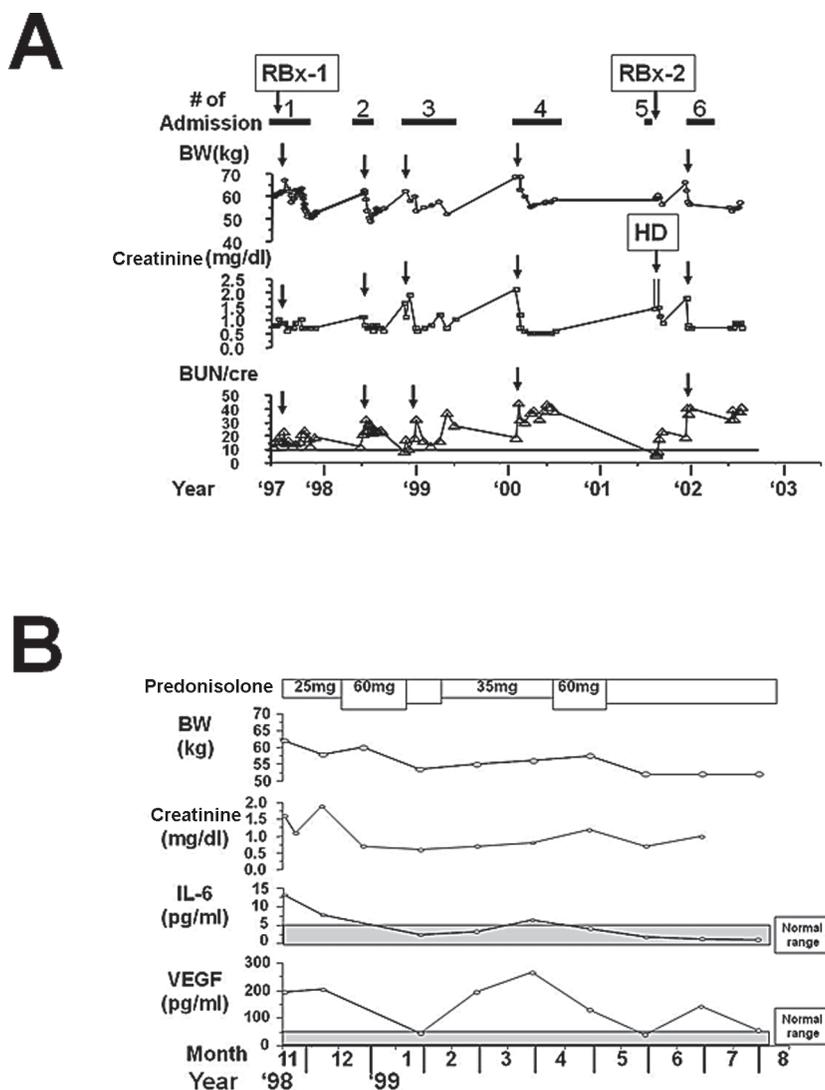


Fig. 1. The scheme of clinical course in this patient.

A. An overview of whole of clinical course showing admission, the time of renal biopsy (RBx), body weight (BW), serum creatinine level and BUN, showing that all of BW, serum creatinine level and serum BUN simultaneously increased and inhibited by administration of methyl-prednisolone. Arrow: administration of methyl-prednisolone. Hemodialysis was performed in the 5th admission before second biopsy.

B. An overview of third admission showed levels of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) in the serum. After decrease of the level of VEGF with increased dose of prednisolone, the elevated levels of VEGF tended to precede the increased BW and serum creatinine level with approximately half a month ahead.

thrombotic microangiopathy (TMA), and glomerular microangiopathy. Among them, a term MPGN-like lesion appear to cover many heterogeneous glomerulopathies associated with mesangial hypercellularity combined with a thickening of the GBM as a common morphological characteristic. Therefore, MPGN-like lesion could include infection-related glomerulonephritis, collagen disease-related glomerulonephritis, paraproteinemia-related glomerulopathies, and TMA such as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (Rennke 1995). Since the glomerulopathy of POEMS syndrome does not contain immune complex and paraprotein, the term MPGN-like lesion is not appropriate to characterize the glomerulopathy

of POEMS syndrome. In addition, TMA may not be an appropriate term for the glomerular lesions of POEMS, because this is the lesion of endothelial injury of the GBM due to microthrombosis resulting in subendothelial edema and mesangiolytic, whereas the chronic endothelial injury of the glomerulopathy of POEMS syndrome does not show the evidence of microthrombosis (Modesto-Segonds et al. 1995).

In addition to the severe subendothelial edema and mesangiolytic with mesangial interposition detected in the present case, marked glomerular enlargement measuring 300 μ m could be found as shown in the literature (Nakamoto et al. 1999). The enlargement of glomeruli can-

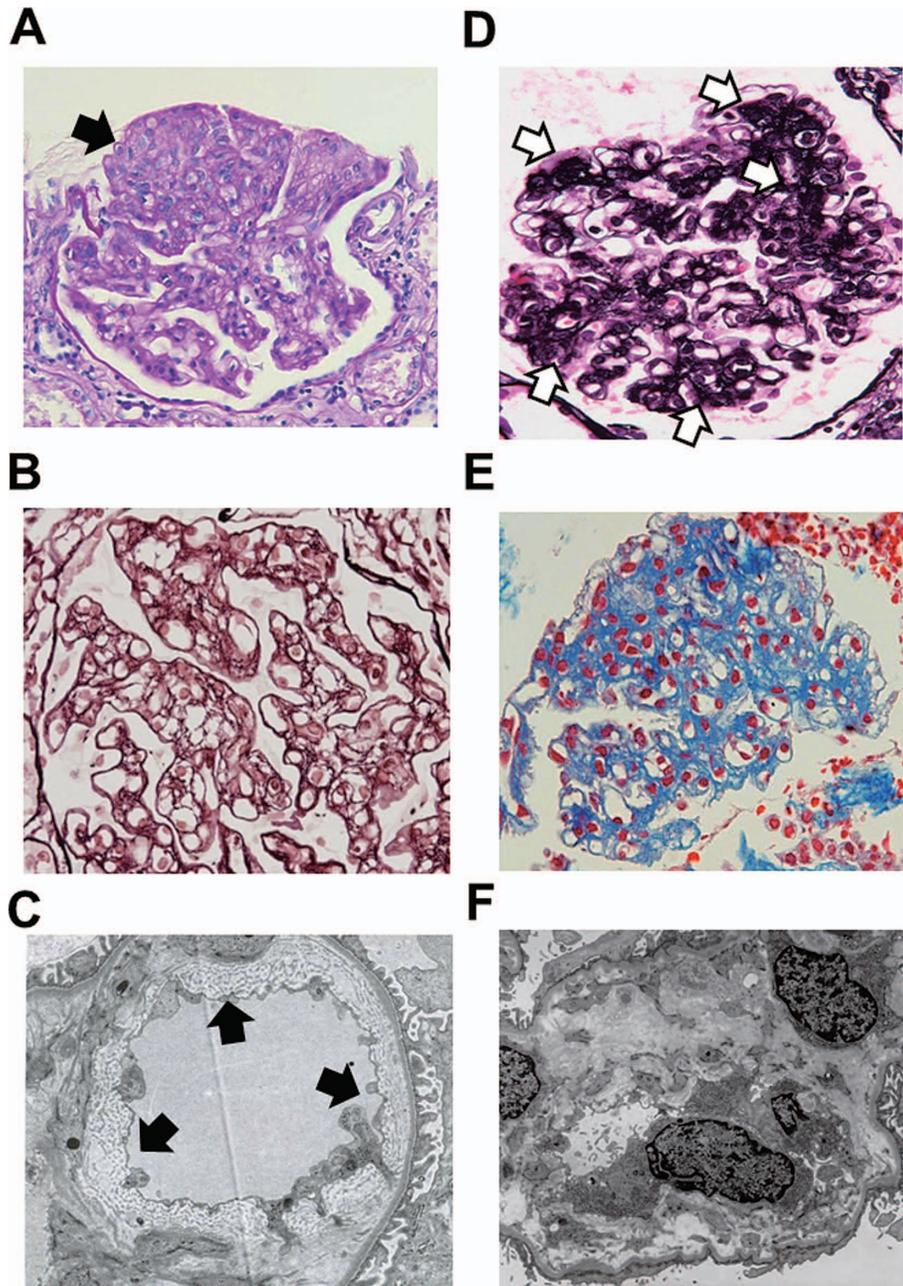


Fig. 2. Histopathological findings in the first and the second renal biopsies.

- A. Focal and segmental lesion consisted of expansion of mesangial matrix and proliferation of glomerular capillary loops resulting in glomerular enlargement ($300\ \mu\text{m}$) was found (arrow) (The first biopsy, PAS stain).
- B. Mesangial matrix expansion and proliferation of glomerular capillary loops inside the expanded mesangial area were demonstrated resulting in double contour of the glomerular basement membrane (The first biopsy, PAM stain).
- C. Severe subendothelial and mesangial expansion, where peculiar fibrillary electron dense material (arrow) was observed by electron microscopy (The first biopsy, original magnification $\times 3,000$).
- D. A progression of mesangial expansion together with an increase of PAM-positive matrix substance (arrow). Irregular thickening of glomerular capillaries with double contour formation was detectable. (The second biopsy, PAM stain).
- E. Widening and sclerosis of mesangial matrix with narrowing of glomerular capillary loops was found (The second biopsy, Masson stain).
- F. Mesangial interposition and increased dense substance became prominent in the extended mesangial and subendothelial spaces. Immature endothels surrounded narrow capillary lumens (The second biopsy, original magnification $\times 3,000$).

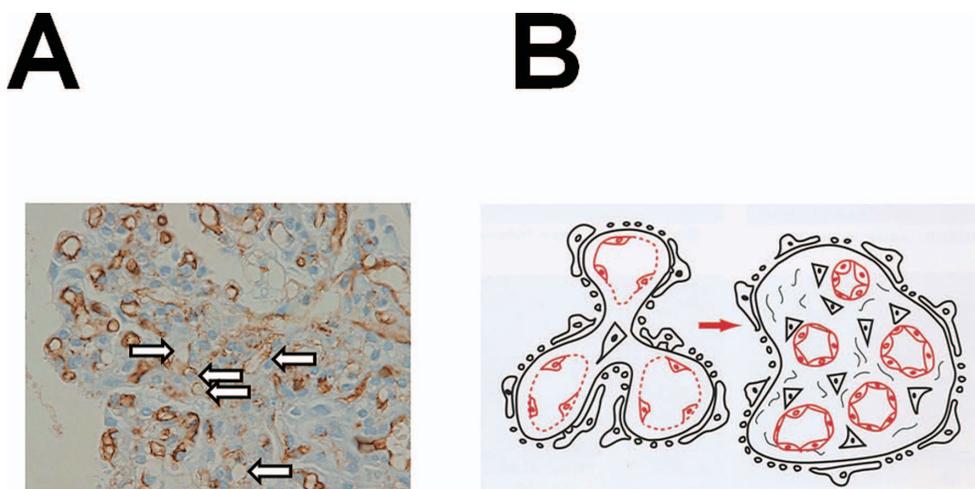


Fig. 3. Immunohistochemical finding and a scheme showing a proliferation of glomerular capillary loops in POEMS syndrome.

A. Immunohistochemical analysis by using anti human CD34 antibody demonstrated that abundant numbers of CD34-positive endocapillaries were found in the expanded mesangial lesion showing both mature and immature (arrow) capillary formations.

B. A scheme shows an increased number of capillaries inside expanded mesangial matrix resulting in enlargement of the glomeruli and reduced diameter of the capillary lumen, which were surrounded by a mixture of mature and immature endothelia was transformed from normal structure of the glomerulus.

not be explained only by endothelial injury resulting in the insudation of the serum into the subendothelial and mesangial matrix, but also explained by proliferation of capillaries as shown in the figure. The number of glomerular capillary loops increased in expanded mesangial area resulting in an enlargement of glomeruli in the present case. As a consequence of the glomerular enlargement, capillary lumens became narrow and were surrounded by mature and immature endothelia, which were documented by using immunohistochemical analysis for CD34-positive cells. The capillary proliferation in the glomeruli may be due to higher serum level of VEGF, because glomeruloid capillary haemangioma as capillary proliferation of the skin found in POEMS syndrome is suspected to be due to the higher serum level of VEGF and IL-6 (Chan et al. 1990).

In addition to the histological findings, fibrillary structure in the subendothelial space and mesangial matrix could be found in electron microscopy in the present case. There have been several reports showing not only fibrillary structure but also small dense granules or flocculent deposits (Fam et al. 1986; Sano et al. 1986; Fukatsu et al. 1991; Kubota et al. 1992; Navis et al. 1994; Higashi et al. 2012). However, the character of the ultrastructural feature showing negative stain for immunoglobulin and complements is not known. Taking account of above-mentioned issues, the glomerulopathy of POEMS syndrome should be appropriately used as the glomerular microangiopathy showing subendothelial edema and mesangiolysis associated with or without mesangial interposition as well as glomerular enlargement with capillary proliferation (Viard et al. 1988; Fukatsu et al. 1991; Modesto-Segonds 1995; Kuwabara et al. 2012).

Previous reports have suggested that POEMS syndrome is associated with high levels of VEGF and IL-6 in serum, ascites, cerebrospinal fluid, and pericardial effusion (Nakazawa et al. 1992; Hitoshi et al. 1994; Gherardi et al. 1996; Watanabe et al. 1996). In the present case, the increased levels of VEGF in the serum correlated with clinical markers such as the severity of anasarca, body weight, and renal dysfunction. Serum level of IL-1 β , IL-6 and VEGF in the patient were 0.699 pg/mL (normal range < 0.567 pg/mL), 8.9 pg/mL (normal < 4.62 pg/mL) and 83.2 pg/mL (normal range < 38.3 pg/mL), respectively. In general, VEGF, IL-6, and IL-12 are cytokines, which show higher level in the serum of POEMS patients and IL-6 but not IL-1 β and TNF α reflected the disease activity (Hitoshi et al. 1994; Kanai et al. 2012). However, in some reports, IL-6 in the ascites (IL-6: 15 pg/mL) in the serum vs. 1,650 pg/mL in the ascites (Nakazawa et al. 1992) or pericardial fluid but not in the serum (IL-6: 6.57 pg/mL) in the serum vs. 1,760 pg/mL in the pericardial fluid and 1,630 pg/mL in the ascites (Shikama et al. 2001) was elevated. However, in some reports, IL-6 in the ascites or pericardial fluid was elevated (Nakazawa et al. 1992; Ako et al. 1999; Shikama et al. 2001). Therefore, it is important to detect not only the cytokines in the serum but also in the pericardial, pleural, and peritoneal fluid.

Other studies have suggested that the pathogenic roles of systemic IL-6 and VEGF in POEMS syndrome should be respected particularly in regards to intrarenal pathological changes such as hyperpermeability, known as systemic capillary leak syndrome (Teelucksingh et al. 1990; Takazoe et al. 1997; Nakamoto et al. 1999; Soubrier et al. 1999; Dispenzieri et al. 2003). Therefore, we hypothesize that the

increased levels of these serum cytokines may be regarded as important factors contributing to an increased permeability of arteriolar wall and glomerular capillaries resulting in severe intimal hyalinosis of the arteriole and severe subendothelial edema of the glomerular capillary walls.

Acknowledgements

The clinical aspects of this manuscript has been presented in the proceeding of Tokyo Renal Biopsy Conference in 2004 (in Japanese), and we obtained permission of publication in English from the publisher. This study was supported by a grant from the committee of "Progressive Renal Diseases" of the Ministry of Health, Labor and Welfare of Japan and Grant-in-Aid for Scientific Research C of the Ministry of Education, Culture, Sports, Science and Technology.

Conflict of Interest

There are no conflict of interest.

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