

AUTOANTIBODIES TO DEK ONCOPROTEIN IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SARCOIDOSIS

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A patient was identified with an unusual auto-immune syndrome consisting of systemic lupus erythematosus and sarcoidosis. Her serum contained extremely high levels of autoantibodies to the DEK protooncogene product. The patient's serum was used to clone a *dek* complementary DNA, which was expressed as a histidine-tagged fusion protein in *Escherichia coli*. Using affinity-purified recombinant DEK protein, anti-DEK autoantibodies were found in the patient's serum at a titer of 1:10⁶ by enzyme-linked immunosorbent assay (ELISA). Longitudinal studies revealed marked variations in anti-DEK autoantibody levels over time. Although it has been suggested that anti-DEK autoantibodies are a marker for pauciarticular juvenile rheumatoid arthritis with iridocyclitis, the present data suggest that they may be associated with other disease subsets as well. The quantitative ELISA technique will be useful for defining these subsets further and for examining the relationship between anti-DEK titers and disease activity.

The DEK oncoprotein is a ubiquitously expressed nuclear protein of uncertain function (1). The *dek* gene on human chromosome 6 is translocated to the *can* gene on chromosome 9 in a subset of patients with acute myeloid leukemia, resulting in the expression of a

truncated DEK-CAN fusion protein (1). It has been reported that DEK is a major autoantigen recognized by sera from patients with juvenile rheumatoid arthritis (JRA) (2). Autoantibodies to DEK are thought to be associated most strongly with pauciarticular-onset JRA with iridocyclitis (3,4). So far, anti-DEK autoantibodies have been detected only by immunoblotting, and little is known about their titers or reactivity with the native DEK protein.

We report here the detection of anti-DEK autoantibodies in serum from a patient with an unusual clinical syndrome characterized by features of systemic lupus erythematosus (SLE) and sarcoidosis. A sensitive enzyme-linked immunosorbent assay (ELISA) based on purified recombinant DEK antigen showed an extremely high titer of autoantibodies to DEK in the patient's serum, indicating that this specificity is not restricted to JRA. The anti-DEK ELISA will be useful for further defining the clinical associations of anti-DEK autoantibodies.

CASE REPORT

In 1982, patient PH, an African American woman, was 18 years old and had an 11-month history of productive cough and erythematous nodular skin lesions of the extremities that evolved into hyperpigmented plaques. She also developed progressive shortness of breath and dyspnea on exertion, dry eyes and mouth, lacrimal gland enlargement, polyarthritis, pleuritic chest pain, and a 9-kg weight loss. There was no occupational exposure to molds, beryllium, or chemicals. Physical examination revealed erythematous nodules and hyperpigmented plaques on her arms and legs, bilateral late inspiratory crackles, and mild hepatosplenomegaly. Oral ulcers, joint symptoms, malar rash, and discoid skin lesions were absent.

Chest radiographs revealed bilateral reticulonodular infiltrates without hilar adenopathy. Pulmo-

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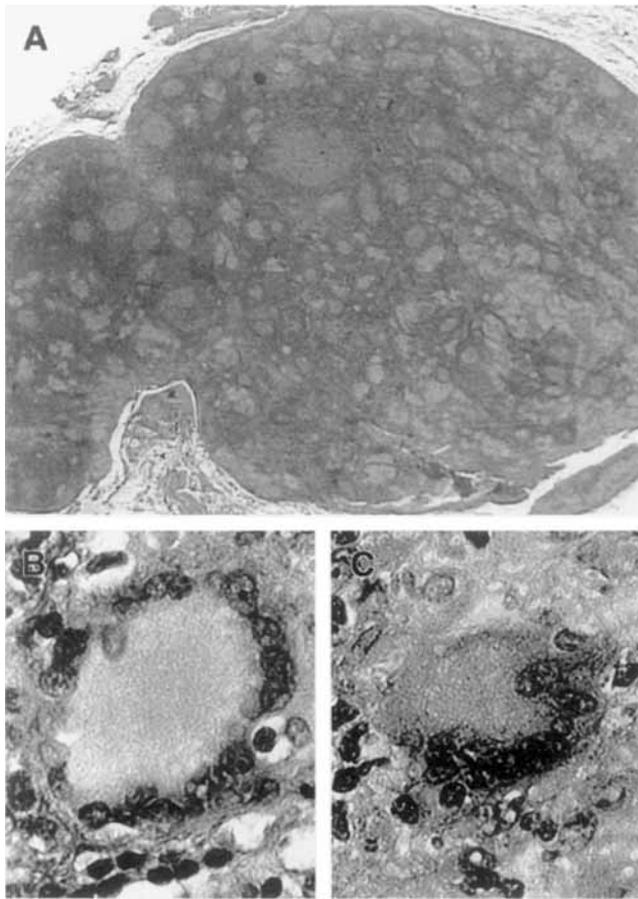


Figure 1. Hematoxylin and eosin–stained sections of a scalene lymph node biopsy obtained in 1982. **A**, Low-power view showing multiple noncaseating granulomas consistent with the diagnosis of sarcoidosis (original magnification $\times 10$). **B** and **C**, High-power views showing multinucleated giant cells (original magnification $\times 400$).

nary function tests were compatible with restrictive disease. The Schirmer test gave positive results; uveitis was absent on slit lamp examination. Scalene lymph node biopsy (Figure 1A) revealed numerous noncaseating granulomas, consistent with sarcoidosis. Multinucleated giant cells were apparent at high power (Figures 1B and C).

Her angiotensin-converting enzyme level was 39 units/liter (normal <30) and lysozyme was 16 $\mu\text{g/ml}$ (normal 2.5–13). Antinuclear antibodies (ANA) at 1:40 were 4+, with a speckled pattern on HEp-2 cell substrate (titer $\geq 1:640$). Anti–double-stranded DNA (anti-dsDNA) antibodies and rheumatoid factor were negative. Anti–nuclear RNP (anti-nRNP), anti-Sm, anti-Ro/SS-A, and anti-La/SS-B antibodies were detected by immunoprecipitation of ^{35}S -labeled proteins and ^{32}P -

labeled small RNAs. Her total hemolytic complement (CH50) level was normal. Her IgG level was 4,110 mg/dl, with normal IgA, IgM, and IgE levels. The erythrocyte sedimentation rate was 77 mm/hour (Westergren), hemoglobin level was 9.9 gm/dl, and hematocrit value was 31.0%. Her creatine kinase level was 540 units/liter. The urinalysis findings and blood urea nitrogen and serum creatinine levels were normal.

The patient was treated with prednisone, 60 mg/day, and the pulmonary symptoms and radiographic findings resolved over a period of 2–3 months. The skin rash also resolved, but new lesions appeared as the prednisone dosage was tapered. Although the patient's initial symptoms and signs were attributable primarily to sarcoidosis, the presence of ANA and anti-Sm antibodies was suggestive of the diagnosis of lupus.

Over the next several years, as the pulmonary involvement resolved, the features of lupus became more prominent. Anti-dsDNA antibodies were first detected in 1984, and increased to 58.5% (by Farr assay) over the next 2 years. Hypocomplementemia (CH50 <16 units/ml) was noted for the first time in 1988. The arthritis became increasingly more severe, and she developed oral ulcers, Raynaud's phenomenon, and migraine headaches thought to be lupus-related. Bilateral carpal tunnel syndrome was diagnosed by electrophysiologic studies in 1988. Mild proteinuria was first noted in 1989.

The erythematous nodular skin lesions continued to reappear whenever the dosage of prednisone was reduced. Hydroxychloroquine, 400 mg/day, was added in an effort to reduce the prednisone dosage, but compliance was poor and the patient continued to have recurrent flares characterized by skin lesions, arthritis, pleuritis, lymphadenopathy/splenomegaly, hypergammaglobulinemia, elevated anti-dsDNA antibody levels, and low CH50 values.

PATIENTS AND METHODS

Patients and sera. The diagnosis of SLE was established using American College of Rheumatology (ACR) criteria (5). The diagnosis of sarcoidosis was based on clinical and histopathologic features (Figure 1) (6). Serial serum samples were obtained from the patient, and serum samples from 3 additional patients who met ACR criteria for SLE and 2 healthy controls were tested in parallel.

Autoantibodies in SLE patient sera were identified by immunoprecipitation of ^{35}S -methionine–labeled K562 (human erythroleukemia) cell extract and con-

firmed by double immunodiffusion as described elsewhere (7). The titer of anti-nRNP/Sm antibodies was determined by antigen-capture ELISA using murine anti-Sm monoclonal antibody Y2 (anti-B'/B and D; gift of Dr. Joan A. Steitz, Yale University, New Haven, CT) to coat the wells, followed by K562 cell extract as a source of U small nuclear RNP (U snRNP) antigen. The wells were incubated sequentially with serial dilutions of human autoimmune serum, a 1:1,250 dilution of alkaline phosphatase-conjugated goat anti-human IgG antibodies, and *p*-nitrophenyl phosphate substrate. The optical density (OD) was determined at 405 nm, and binding of the serum to Y2 alone was subtracted.

DEK complementary DNA (cDNA) clone. Serum from patient PH was used to obtain a human *dek* cDNA clone from a HeLa UniZap XR cDNA expression library (Stratagene, La Jolla, CA). Clone 15.2 contained a 1.2-kb insert with a sequence matching the previously reported DEK sequence (1). The cDNA sequence contains the entire coding region for DEK protein. The 1.2-kb insert was subcloned into the *Eco* RI site of Bluescript II SK+ (Stratagene), excised with *Bam* HI plus *Bgl* II, and inserted in-frame behind the His⁶ tag and thrombin cleavage sequences of the 6HisT pET 11d vector (Novagen, Madison, WI). This permitted expression of a histidine-tagged recombinant DEK protein.

Antigen expression and purification. Fusion protein expression was induced by growing transformed bacteria in LB medium at 37°C for 3 hours, adding 0.1 mM isopropyl- β -D-thiogalactoside (IPTG), and incubating for an additional 3 hours. The bacterial pellets were resuspended in NET-NP40 lysis buffer (0.15M NaCl, 50 mM Tris, pH 7.5, 2 mM EDTA, 0.3% Nonidet P40) containing 0.5 mM phenylmethylsulfonyl fluoride and 0.3 trypsin inhibitor units/ml of aprotinin, and sonicated on ice. The lysate was cleared by centrifuging twice at 12,000g for 10 minutes before loading the cleared lysate onto ProBond Ni columns (Invitrogen, San Diego, CA). The column was washed 3 times with lysis buffer, then with washing buffer (0.5M NaCl, 20 mM sodium phosphate, pH 7.8) containing 10 mM imidazole, followed by washing buffer containing 20 mM imidazole. The fusion protein was eluted with washing buffer containing 100 mM imidazole.

Purity was verified by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis. The antigen was shown to consist of a major band migrating at ~50 kd and a minor band of ~40 kd in Coomassie blue-stained gels. Both of these bands were reactive with serum from patient PH on immunoblots (see Figure 2A).

Immunoblotting. Western blot analysis of anti-Sm and anti-nRNP antibodies was performed using affinity-purified U1 snRNP as described previously (7). For analysis of anti-DEK antibodies, affinity-purified His⁶-DEK fusion protein was fractionated on 10% SDS-polyacrylamide gels and transferred to nitrocellulose. The membrane was blocked with 5% nonfat dry milk in phosphate buffered saline, and then incubated for 1.5 hours with human serum (1:500 dilution) or mouse anti-His monoclonal antibody (1:1,000 dilution). Second antibodies were alkaline phosphatase-conjugated goat anti-human or mouse IgG, respectively (1:1,000 dilution for 1.5 hours). Blots were developed with nitroblue tetrazolium/BCIP (Bio-Rad, Richmond, CA).

Anti-DEK ELISA. An ELISA for detecting antibodies to DEK was developed using affinity-purified His⁶-DEK fusion protein. The wells of microtiter plates were coated overnight at 4°C with affinity-purified fusion protein at 2 μ g/ml in 20 mM Tris HCl, pH 8.0, washed twice, and blocked with borate buffered saline (0.17M H₃BO₃, 0.12M NaCl, pH 8.5) containing 0.5% bovine serum albumin, 1 mM EDTA, 0.05% Tween 20. The wells were incubated with patient serum at 1:250 dilution for 1.5 hours at 22°C. After washing again, alkaline phosphatase-conjugated goat anti-human IgG (γ chain-specific; 1:1,250 dilution) was added for 1.5 hours. The wells were washed, *p*-nitrophenyl phosphate substrate was added, and the OD at 405 nm was determined.

RESULTS

Autoantibodies to the protooncogene DEK have been reported in sera from JRA patients, and it has been suggested that these antibodies are a marker for a subset of JRA (2-4). So far, anti-DEK antibodies have been detected only by western blot, and their titers and reactivity with the native antigen are unknown. A cDNA encoding the full-length human DEK was cloned using serum from a patient who had an unusual autoimmune syndrome, with features of both SLE and sarcoidosis. A recombinant fusion protein was used to examine the autoimmune response to native DEK.

Immunoblot analysis of serial serum samples from patient PH. A histidine-tagged DEK fusion protein was expressed in *Escherichia coli* as described in Patients and Methods. As shown in Figure 2A, serial samples of serum obtained from patient PH from November 1982 through May 1991 exhibited strong reactivity by western blot with affinity-purified ~50-kd DEK fusion protein and weaker reactivity with an ~40-kd degradation product. Normal human serum was unreactive.

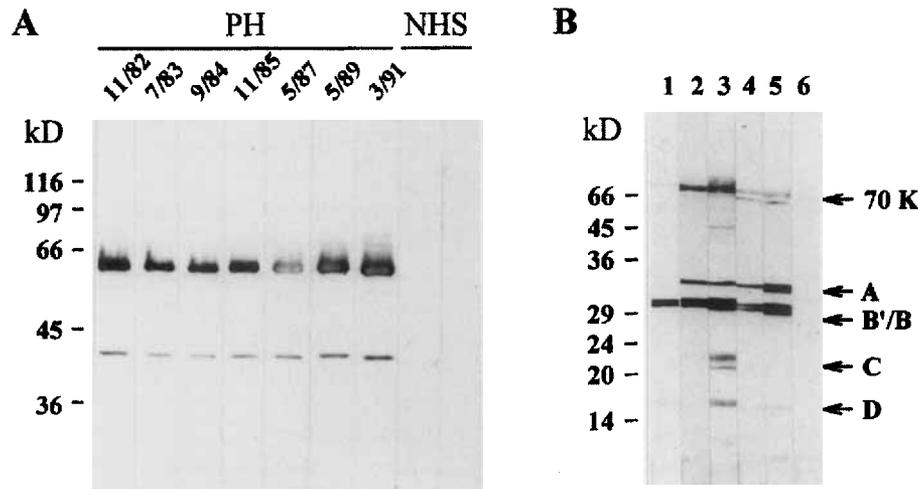


Figure 2. Immunoblot analysis of anti-DEK antibodies and anti-nuclear RNP (anti-nRNP)/Sm antibodies. **A**, His⁶-DEK fusion protein was affinity purified, fractionated on a 10% sodium dodecyl sulfate-polyacrylamide gel, and transferred to nitrocellulose. Strips cut from the blot were probed with serial samples of patient PH serum obtained between November 1982 and March 1991 or with normal human serum (NHS) at a dilution of 1:500, followed by alkaline phosphatase (AP)-conjugated goat anti-human IgG (1:1,000 dilution). Molecular weight markers are shown at the left. **B**, U snRNPs were affinity purified from K562 cells (human erythroleukemia) and transferred to nitrocellulose membrane. Strips of the membrane were probed with murine monoclonal antibody Y2 (anti-Sm B'/B and D, lane 1), human anti-nRNP prototype serum (lane 2), human anti-nRNP + Sm prototype serum (lane 3), patient PH serum obtained in November 1982 (lane 4), patient PH serum obtained in May 1991 (lane 5), and normal human serum (lane 6). Sera were diluted 1:500, and binding of antibodies was detected with AP-conjugated goat anti-human IgG antibodies. Y2 was used as undiluted culture supernatant, and antibody binding was detected with goat anti-mouse IgG antibodies. Positions of the U1-70K, A, and C proteins, as well as the Sm-B'/B and D proteins are shown at the right; molecular weight markers are shown at the left.

In double-immunodiffusion studies, serum PH was found to contain Sm, nRNP, Ro/SS-A, and La/SS-B autoantibodies. The titer of anti-nRNP/Sm activity was 1:625,000 by ELISA. The patient's sera had high levels of anti-nRNP and anti-Sm antibodies by western blot, consistent with the results of the immunodiffusion studies (Figure 2B). Serum samples obtained in November 1982 and May 1991 both recognized the U1-A and U1-70K proteins as well as with the Sm-B'/B and D proteins (Figure 2B, lanes 4 and 5, respectively).

By an immunoprecipitation assay that discriminates between anti-nRNP and anti-Sm (7), the patient's sera recognized the intact Sm core particle (anti-Sm) as well as the U1-A and U1-C nRNP proteins (results not shown). Also apparent in the immunoprecipitates were a series of more slowly migrating proteins, the mobilities of which were consistent with those of the 45-kd La/SS-B and 60-kd Ro/SS-A proteins. These specificities were confirmed by ³²P RNA immunoprecipitation (results not shown). Thus, in addition to anti-DEK antibodies, sera

from patient PH contained nRNP, Sm, Ro/SS-A, and La/SS-B antibodies.

Titer of anti-DEK antibodies in patient PH serum. Human autoantibodies have not previously been shown to recognize the native DEK protein, nor have the titers of these antibodies been determined. To examine the reactivity of the patient's serum with native antigen, recombinant DEK was purified and used in an ELISA.

The binding of PH serum, as well as sera from 3 anti-DEK immunoblot-negative SLE patients and 2 healthy subjects, to the DEK fusion protein was determined by ELISA (Figure 3A). The titer of anti-DEK autoantibodies in PH serum was $\sim 1:10^6$. In contrast, the binding of the 3 anti-DEK-negative SLE sera was similar to that of the 2 normal human sera. The titer of anti-native DEK antibodies by ELISA (Figure 3A) was comparable to the titer by immunoblot, suggesting that the major epitope(s) is relatively insensitive to denaturation (results not shown).

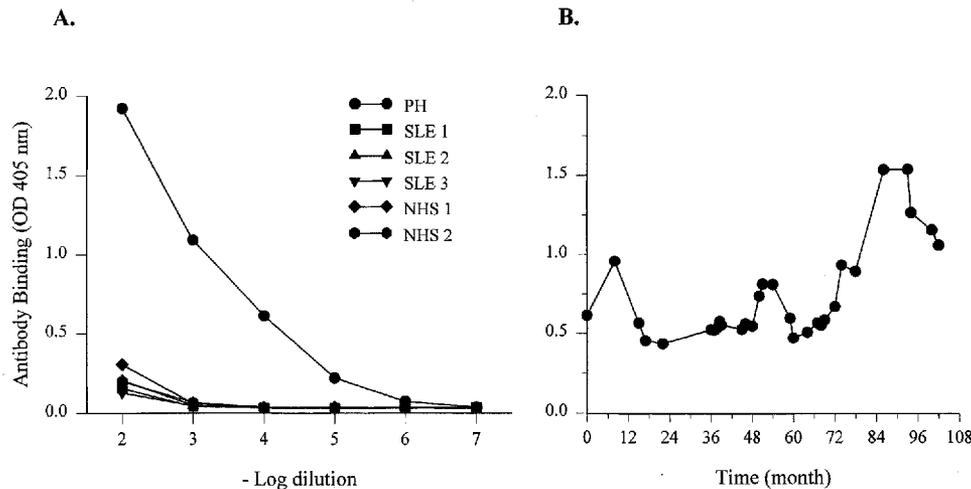


Figure 3. Anti-DEK enzyme-linked immunosorbent assay (ELISA). **A**, Titer of anti-DEK antibodies. Human sera were tested for antibodies to DEK by ELISA using affinity-purified His⁶-DEK fusion protein. Serum obtained in July 1988 from patient PH was tested at 10^{-2} , 10^{-3} , 10^{-4} , 10^{-5} , 10^{-6} , and 10^{-7} dilutions. Sera from 3 additional patients with systemic lupus erythematosus (SLE 1, 2, and 3) that were negative for anti-DEK by immunoblot assay were tested at the same dilutions, along with 2 normal human sera (NHS 1 and 2). Second antibody was alkaline phosphatase-conjugated goat anti-human IgG (1:1,250 dilution). **B**, Variation of anti-DEK antibody levels over time. Anti-DEK activity was determined by ELISA in serial serum samples obtained from patient PH from November 1982 through May 1991. Sera were tested at a 1:250 dilution, and the optical density (OD) is presented as a function of time (months) after the initial serum sample.

A longitudinal study of anti-DEK antibody levels was carried out using patient PH sera obtained from November 9, 1982 through May 6, 1991 (Figure 3B). The peak anti-DEK level occurred between January and August 1990. At that time, the patient's total IgG level of 4.4 gm/dl was similar to that on November 11, 1982 (4.1 gm/dl) and on January 17, 1989 (4.4 gm/dl), suggesting that the increased levels of anti-DEK antibodies were not merely a consequence of increased polyclonal hypergammaglobulinemia. The pulmonary disease had largely resolved by that time, but the lupus was active, with prominent arthritis, skin rashes, palpable spleen, increasing IgG levels, and hypocomplementemia. Analysis of a recent serum sample (December 1997) revealed that the levels of anti-DEK antibodies returned to their baseline level (results not shown).

DISCUSSION

The DEK protooncogene product has been reported to be a major autoantigen in JRA (2,3). Autoantibodies to DEK may be a marker of pauciarticular-onset JRA with iridocyclitis (4). However, detailed studies of the clinical associations of these autoantibodies are not available. We report the case of a patient

with the unusual coexistence of SLE and sarcoidosis whose serum contained high levels of anti-DEK antibodies. A *dek* cDNA was isolated using the patient's serum, and a sensitive ELISA based on recombinant DEK was developed. The titer of anti-DEK autoantibodies in the serum was $\sim 1:10^6$, suggesting that extremely high levels of these autoantibodies can be produced in the absence of either JRA or iridocyclitis.

The anti-DEK ELISA makes possible large-scale screening of human sera, permitting more definitive evaluation of the clinical significance of anti-DEK autoantibodies. In particular, the ELISA will be useful for examining whether these autoantibodies are a marker for iridocyclitis or a pathologic process associated with iridocyclitis. Preliminary data suggest that anti-DEK autoantibodies are associated with SLE, sarcoidosis, tuberculosis, and other disorders, as well as JRA (8). Thus, it seems unlikely that anti-DEK antibodies are a diagnostic marker for JRA. On the other hand, iridocyclitis may be associated with a variety of disorders, including both JRA and sarcoidosis. However, it is often granulomatous in sarcoidosis, but characteristically non-granulomatous in JRA (9). Although granulomatous uveitis complicates sarcoidosis about 25% of the time,

there was no evidence for it on slit lamp examination, despite the presence of extensive noncaseating granulomas in other tissues (Figure 1).

Despite the different histopathologic findings in uveitis associated with JRA versus sarcoidosis, epithelioid macrophages and giant cells are common in both conditions (10,11). In sarcoidosis, these cells play a key role in granuloma formation, act as competent accessory cells, and express high levels of the costimulatory molecule B7-1 (CD80) (12). Tumor necrosis factor α (TNF α) plays a critical role in the formation of granulomas in sarcoidosis and other conditions (13). In view of previous reports that autoimmunity can be induced by local inflammation mediated by TNF α plus abnormal B7-1 expression (14), it can be speculated that increased expression of B7-1 and/or TNF α by epithelioid macrophages in JRA and sarcoidosis might contribute to the development of uveitis, the high frequency of ANA in JRA with uveitis (15), and possibly, the clinical association of sarcoidosis with SLE. Patient PH developed SLE and sarcoidosis nearly simultaneously. Although unusual, this association has been reported previously (16). The simultaneous onset of lupus and sarcoidosis is consistent with the possibility that there could be overlap in the pathogenetic mechanisms of these disorders.

In conclusion, we report the production of extremely high levels of autoantibodies to the DEK protooncogene protein in a patient with the near-simultaneous onset of sarcoidosis and SLE. The data provide evidence that there may be overlap in the events involved in the pathogenesis of lupus and granulomatous diseases. Anti-DEK autoantibodies could reflect these events. However, more in-depth studies of the significance of anti-DEK autoantibody production are needed. The recombinant DEK ELISA will facilitate these studies by allowing large-scale screening of human sera and quantitation of the levels of anti-DEK antibodies.

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