Generalized Granuloma Annulare Associated with *Borrelia burgdorferi* Infection and p83 Gene-A Potential Relation to the Phenomenon of Molecular Mimicry and Heat-Shock Proteins? Case Report

Borrelia burgdorferi Enfeksiyonu ve p83 Geni ile İlişkilendirilmiş Jeneralize Granüloma Anülare-Moleküler Benzerlik Fenomeni ve Isı-Şok Proteinleri ile Olası İlişkisi?

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ABSTRACT Lyme disease is a multysystemic infectious disease caused by spirochetes called "*Borrelia burgdorferi*", as a result of tick bite. Except the typical clinical lesions, a few granuloma annulare associated with borrelia infection have been reported, in recent years. In this report, presented a 52-year-old woman with generalized granuloma annulare. According to the medical history, the patient was bitten by a tick one year ago. Other clinical examination, routine hematological and biochemical investigations of patients were normal ranges and performed cutaneous biopsy was compatible with granuloma annulare. Borrelia IgM was positive and IgG was negative in the enzyme-linked immunosorbent assay (ELISA) tests, which were examined in the peripheral blood. Additionally, in the Western Immunoblotting (WB) tests for the purpose of verifying the result, borrelia IgM was positive (against specific membran vesical protein p83) and IgG was negative. Based on these findings, cutaneous lesions are thought to be associated with borrelia infection and the patient was treated with doxycycline (200 mg/day, for 14 days). No additional treatment or topical treatment were applied to the patient. Whole lesions of the patient, completely disappeared, two and half months after the initiation of treatment. The patient was presented because of any case of generalized granuloma annulare associated with borrelia infection and p83 gene have been reported in the literature previously. And, a probable crossed–mediated reaction from T-cell type which might have induced the rare type of granuloma annulare, is discussed through the concepts of "heat-shock proteins (Hsps)" and "molecular mimicry". Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Key Words: Borrelia burgdorferi; generalized granuloma annulare; lyme disease; molecular mimicry; heat-shock proteins

ÖZET Lyme hastalığı, "*Borrelia burgdorferi*" (Bb) adı verilen spiroketin, kene ısırığıyla bulaşı sonucu gelişen multisistemik bir enfeksiyon hastalığıdır. Tipik klinik lezyonlar dışında son yıllarda az sayıda borelya enfeksiyonu ile ilişkilendirilen granüloma anülare olguları bildirilmiştir. Bu makalede, hikayesinde bir yıl önce bir kene tarafından ısırıldığını belirten, jeneralize granüloma anülareli, 52 yaşında bir kadın hasta sunulmuştur. Diğer klinik muayeneleri, rutin hematolojik ve biyokimyasal tetkikleri normal sınırlarda olan hastanın lezyonlarından yapılan deri biyopsisi granuloma anülare ile uyumluydu. Periferik kandan yapılan enzyme-linked immunosorbent assay (ELISA) testlerinde, boreIya IgM pozitif ve borelya IgG negatif olarak tespit edildi. Doğrulama testi olarak yaptırılan Western Immunoblotting (WB) testlerinde ise borelya IgM (spesifik membran vezikal proteini p83'e karşı) pozitif ve IgG negatifti. Bu bulgularla, kütanöz lezyonların borelya enfeksiyonu ile ilişkili olabileceği düşünülerek, hasta doksisiklin ile tedavi edildi. (200 mg/gün, 14 gün). Herhangi bir ek tedavi ya da topikal tedavi uygulanmadı. Lezyonlar tedavi başlandıktan 2,5 ay sonra tamamen geriledi. Literatürde, borelya enfeksiyonu ve p83 geni ile ilişkilendirilmiş, jeneralize granuloma anülare daha önce bildirilmemiş olduğundan olgumuz sunuma uygun bulunmuş ve granuloma anülarenin bu nadir tipinin gelişiminde, T-hücre tipi çapraz reaksiyonun olası etkisi "Isı-şok proteinleri (heat-shock proteins-Hsps)" ve "moleküler benzerlik" kavramları üzerinden irdelenmiştir. Hastamızdan, hastalığıyla ilgili bilgi ve fotoğrafların bu yayında kullanılabileceğine ilişkin aydınlatılmış yazılı onam alınmıştır.

Anahtar Kelimeler: Borrelia burgdorferi; jeneralize granüloma anülare; lyme hastalığı; moleküler benzerlik; ısı-şok proteinleri

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Lyme diseases is a multisystemic infectious disease caused by tick-transmitted spirochetes of the Borrelia burgdorferi.[1] The three characteristic cutaneous manifestations are erythema chronicum migrans, lymphadenosis benigna cutis, and acrodermatitis chronica atrophicans progressiva Herxheimer.[1-3] Besides the classical manifestations of cutaneous borreliosis, evidence is growing that at least in part also other skin manifestations, especially morphea, lichen sclerosus and cases of cutaneous B-cell lymphoma are causally related to infections with borrelia.[2-5] There are also single reports of other skin manifestations to be associated with borrelia infections like cutaneous sarcoidosis, necrobiosis lipoidica, necrobiotic xanthogranuloma, systemic sclerosis, eosinophilic fasciitis, lichen sclerosus et atrophicus, atrophoderma of Pasini and Pierini, pseudolymphoma, septal panniculitis resembling erythema nodosum, progressive facial hemiatrophy of Parry-Romberg and sclerodermatous porphyria cutanea tarda.[3-6] Also granuloma annulare and interstitial granulomatous dermatitis might be partly caused by Borrelia burgdorferi or similar strains.[3,5-12]

Despite the pathogenesis of generalized granuloma annulare has not been fully elucidated, the presence of activated T-cells in the lymphocytic infiltrate of granuloma annulare has been demonstrated; suggesting there is a cell-mediated immune response to various precipitating factors.[13] In a similar fashion, cutaneous sarcoidosis is characterized by a macrophage/T helper-1 cell-mediated, non-caseating, granulomatous inflammation process.[14] Tchernev and et al. has been stated that an autoimmune etiology of sarcoidosis could possibly occur through a process of molecular mimicry of infectious or other environmental antigens to host antigens and this could lead to a cross-mediated immune response and induction of autoimmune disease.[15]

CASE REPORT

A 52-year-old woman had been in good health until ten month ago. According to the medical history, the patient was bitten by a tick one year ago. Two months after the thick bite, a reddish papule occured on the right hand of the patient. The papule gradually increased in size and acquired an irregular ring-shaped form with a diameter of about 15 cm, within 3 months. During this time, a similar lesion emerged on the left hand. Thereafter, similar cutaneous lesions spread to other parts of the body, especially to the arms and forearms.The patient had been treated several times with topical and systemic steroids and antihistamines, but was not healed. She had no history of erythema migrans. There was no history of drug use or vaccination.

The patient admitted to us because of gradually spreading skin lesions. In the dermatologic examination, there was a big, reddish, 16 cm diameter plaque on the right hand (Figure 1), and, another reddish, 14.5 cm diameter plaque on the left hand (Figure 2). There was some atrophy on the surface of the plaques. Additionally, there were numerous small papules or rings on the arms, which ranged from 6 mm to 38 mm in diameter (Figure 3).

Physical examination of the patient established no other abnormalities than the cutaneous changes. The patient did not have any systemic symptoms like malaise, fatigue, headache, arthral-

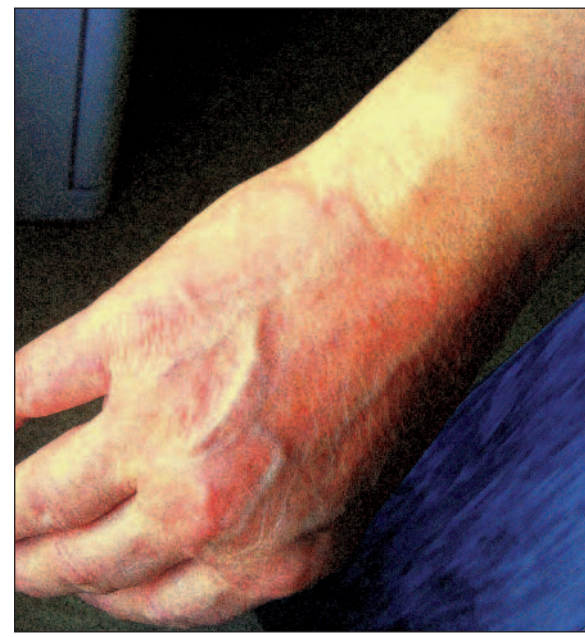

FIGURE 1: Right hand plaque.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

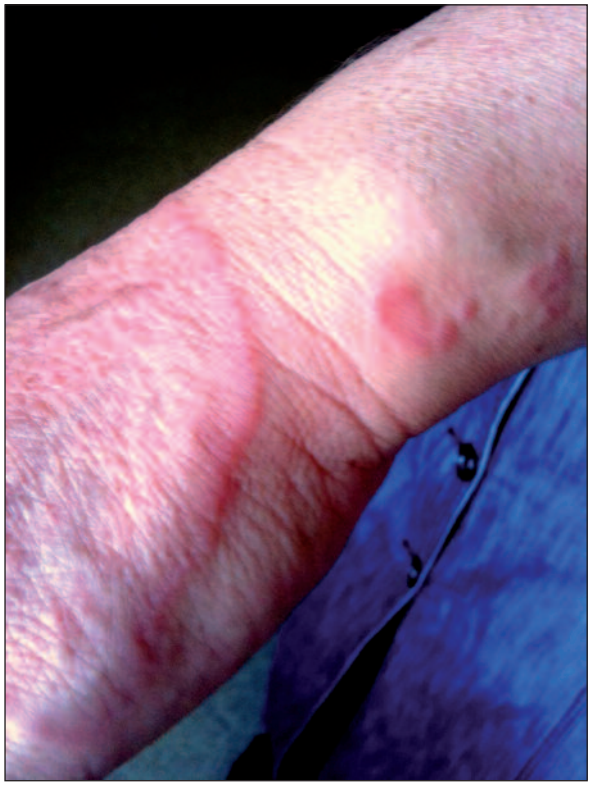

FIGURE 2: Left hand plaque.
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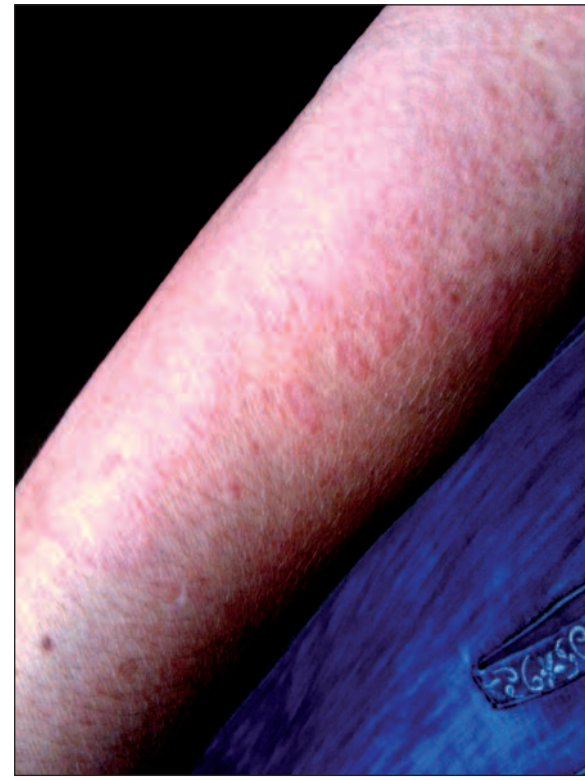

FIGURE 3: Numerous papules and plaques on the right arm.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

gia, myalgia, fever and, regional lymphadenopathy suggesting a systemic dissemination of the pathogen, and did not have pruritus.

In the laboratory parameters; complete blood cell count, erythrocyte sedimentation rate, concentration of proteins, urea and creatinine levels, liver function tests [ALT:27 U/L (reference values:10-49 U/L), AST:28 U/L (reference values:0-34 U/L), and GGT:15 U/L (reference values:12-23 U/L)], glucose, concentrations of electrolytes, C-reactive protein, serologic examinations of syphilis, anti-HIV antibodies, markers of hepatitis, rheumatoid factor, antinuclear antibody [ANA:<1/100 (reference values: <1/100=negative, 1/100=weak positive, >1/100=positive) with ANA Europlus™ mosaic 20A, EUROIMMUN ANA test], TSH, FT3, FT4, tumor markers and urine tests were all within normal limits. A chest X-ray and abdominal ultrasound were both normal.

In the ELISA tests, borrelia IgM was borderline positive [16.2 RU/mL (cut-off value: 16 RU/mL), Evaluation of ELISA tests: <16 RU/mL= negative, 16-22 RU/mL=borderline positive, ≥22 RU/mL=positive] and borrelia IgG was negative [2 RU/mL (cut-off value: 16 RU/mL) with EUROIMMUN Anti-borrelia ELISA test, Medizinische Labordiagnostika AG, Lübeck, Germany, MNT laboratories/Istanbul]. In the western immunoblotting (WB) tests to confirm these results, also IgG was negative, and, IgM was strong positive against spesific membran vesical protein "p83" [Evaluation of WB tests: 2 band positivity=strong positive, 1 band positivity=positive, band negativity=negative (with EUROIMMUN Anti-borrelia EUROLINE test, Medizinische Labordiagnostika AG, Lübeck, Germany, IMD laboratories/ Berlin)]. Immune responses to other antigens of *Borrelia burgdorferi* (VLsE, p17, p19, p21,Ops C , p30, Ops A, p39) were negative. PCR assay from the cutaneous lesions could not be made due to insufficient financial conditions of the patient.

Performed cutaneous biopsy was compatible with granuloma annulare. There was a palisade-

patterned granuloma with a central zone of necrobiotic collagen surrounded by a palisade of histiocytes and some lymphocytes (Figure 4).

Based upon the clinical, histopathological and immunological findings, a diagnosis of generalized granuloma annulare associated with borrelia infection, was made. The patient was treated with oral doxycycline for 14 days (200 mg/day). No additional systemic treatment or topical treatment was applied to the patient. The patient was checked weekly. Any adverse effects were observed during the treatment. The lesions gradually decreased from the third week. Whole lesions of the patient expired completely, two and half months after the initiation of treatment. The patient has yet to follow up.

DISCUSSION

Granuloma annulare, is an idiopathic and benign granulomatous disorder with classic features including single or multiple papules with a tendency to form annular lesions. There is a wide spectrum of clinical subsets including localized, generalized, perforating, subcutaneous and erythematous types.[16-20] The generalized form was described in 1973 by Duncan et al.[21] Approximately 15% of patients have more than 10 lesions and are thus considered to have generalized granuloma annulare.[22] It has been known that generalized granuloma annulare occurs in about 8-15% of all types of granuloma annulare, mostly in adults in their 50's and predominantly in women aged 30 to 70 years old.[17] Numerous cutaneous lesions of our patient were clinically consistent with generalized granuloma annulare. Our patient had no history of erythema chronicum migrans during the disease. However, at the site of the tick bite, an erythema chronicum migrans can be absent in up to 20 to 50% of patients.[23]

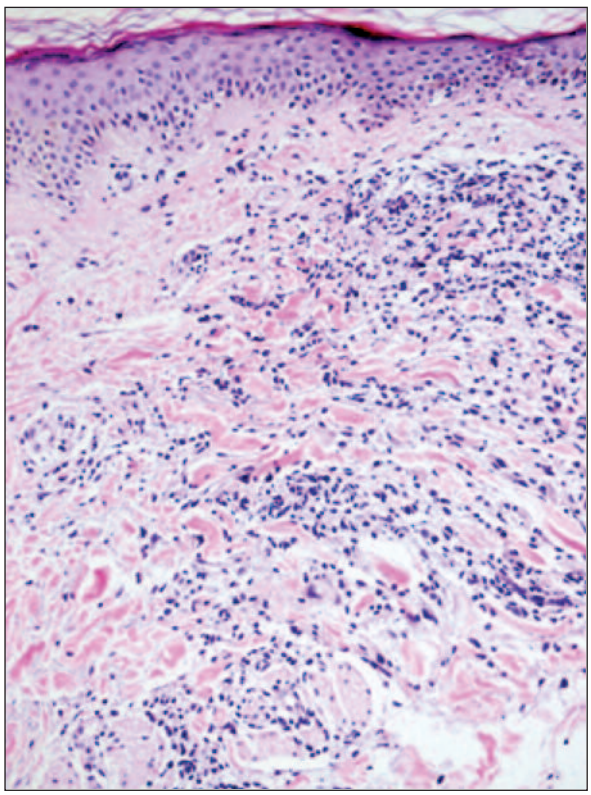

FIGURE 4: Histopathology of the granuloma (HEx100).
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In the course of the Lyme disease there has not yet been defined a specific stage for generalized granuloma annulare. Only, Strle et al. stated that, emergence of the lesions of granuloma annulare can begin two months after the tick bite, and the duration of them can take up to one year after the tick bite.[12] The time of the emergence of the lesions of our patient, was compatible with the literature. The IgM antibodies were still positive and the IgG antibodies were still negative, even twelve months after the tick bite. Therefore we thought that the patient was in the acute phase of the borrelia infection, because borrelia IgM rise 2-4 week after the tick bite and may persist at high levels for many years. Moreover, borrelia IgG might not rise until many years after the tick bite.[24,25]

Although the pathogenesis of generalized granuloma annulare is unknown, it has been described in patients with diabetes mellitus, malignancies, thyroid diseases, hepatitis B and C virus infections, acquired immunodeficiency syndrome.[16-19] Also, it has been reported that granuloma annulare occurred following an insect bite, sun exposure, BCG vaccination and some medications.[26-28] Granuloma annulare has also been observed in individuals with deficiencies in cell-mediated immunity, such as patients with sarcoidosis.[29] It has been suggested that a T-cell-

mediated delayed-type hypersensitivity response is the cause of the granuloma annulare.[29,30] Fayyazi et al. have suggested that in granuloma annulare, interferon-gamma+Th-1 lymphocytes may cause a delayed-type hypersensitivity reaction whereby macrophages that differentiated to aggressive effector T-cells expressing tumor necrosis factor-alpha and matrix metalloproteinases.[30] On the other hand, in the Lyme disease, cases have been reported with no significant B cell response although specific T-cell proliferative responses were detected.[24]The pathogenesis of granuloma annulare appears likely that it represents a reaction pattern to a variety of triggering factors.[31,32] In our case we did not find another reason that may be responsible for the etiology of the granuloma annulare, except the borrelia antibodies.

The relationship between granuloma annulare and *Borrelia burgdorferi* is not a new topic in the literature.[8,12,14,15,33] The isolation by culture of *Borrelia* from a granuloma annulare in a patient with borderline serologic titres for *Borrelia burgdorferi* was reported by Strle et al. in 1991.[12] In 2008, Ziemer et al. reported that borrelia antibodies were detected in 127 of 157 biopsies of localized granuloma annulare, and, they reported that borrelia might have taken a role specifically in the aetiology.[8] On the contrary, Zollinger et al. reported that borrelia DNA was detected in one of 48 granuloma annulare biopsies and stated that, their results and PCR-based studies until 2009, had not argued for a significant association of borrelia with granuloma annulare.[5] *Borrelia burgdorferi* is difficult to detect in routine biopsy material from patients with cutaneous lesions of borreliosis.[34] Cultivation of borrelia from a patient's skin or blood is the gold standard for demonstration of active infection, but it is expensive and lacks clinical sensitivity.[35] Detection of spirochetal DNA in clinical samples by PCR has better sensitivity, but PCR for *Borrelia burgdorferi* has not yet been standardized for more routine diagnostic testing.[35,36] Detection of antibodies to *Borrelia burgdorferi* is the most practical and common approach for laboratory work-up of a case of suspected Lyme disease.[35] Serologic assays fall short of 100% sensitivity and specificity. Although new subunit serologic assays based on recombinant proteins are becoming available commercially, the longstanding two-test approach in which a positive or indeterminate result with a standardized, sensitive ELISA test is followed by verification with a more specific WB assay, still provides the physician with a reasonably accurate and reliable assessment of the presence of antibodies to Bb.[35,36]

In our case, we determined specific IgM antibodies against *Borrelia burgdorferi* in both tests, as well. The borrelia IgM was strong positive against specific membran vesical protein "p83" in the WB test. The "p83" of *Borrelia burgdorferi* is a chromosomal gene which is coded for an 83-kDa highly immunogenic polipeptide.[37] This molecule with sequences from protein databases has been shown to have similarities with characteristics of eukaryotic cell structures. The p83 might mimic these structures and may, therefore, be involved in the immune escape mechanism of the pathogenic agent of Lyme disease.[38]

On the other hand, all organisms respond to elevated temperatures by altering their pattern of growth and protein synthesis. Upon exposure to elevated temperatures, cells rapidly cease growth, repress the synthesis of many vegetative proteins, and coordinate and preferentially synthesize a small number of highly conserved proteins. This is termed the "heat shock response".[39] Autoreactivity is based on antigenic cross-reactivity between epitopes common to borrelia and a human host, especially situated on so called "heat shock proteins (Hsps)".[39,40] Many Hsps of *Borrelia burgdorferi* have been identified such as p60, p66, p43, p72, p24, p35, p28.[38-40]

Two Hsps in particular, Hsp7l and Hsp65 have been shown to be major antigens in *M. tuberculosis* and *M. leprae*. These two immunodominant Hsps appear to be involved in both humoral and cellular immunity . Additionally, it has been suggested that antibodies to these proteins may react with homologous host proteins to produce autoimmune pathologies such as arthritis. These observations argue that a similar situation may exist in

Lyme disease.[39] In a further aspect, molecular mimicry is one mechanism by which infectious agents trigger an immune response against the host antigens. When a susceptible host acquires an infection with an organism that has antigens immunologically similar to the host antigens but differ sufficiently, to induce, an immune response when presented to T cells, it results in a loss of tolerance to host antigens. Furthermore there is development of a pathogen-specific immune response that cross-reacts with host structures to cause tissue damage and disease.[41-43]

Several diseases have been reported to be possibly associated with the mechanism of molecular mimicry, such as insulin-dependent diabetes, multiple sclerosis, myasthenia gravis, pemphigus, Lyme diseases, syphilis, celiac disease, autoimmune uveitis.[42,44] For example an autoimmune etiology of sarcoidosis could possibly occur through a process of molecular mimicry of infectious or other environmental antigens to host antigens. This, could lead to a cross-mediated immune response and induction of autoimmune disease.[14,15]

Based on this information, we suggest that an antigen mimicry may be responsible for the clinical picture of this rare type of granuloma annulare. In this picture, a crossed-mediated reaction from T-cell type might have been developed between host proteins and borrelia antigens, and, the protein "p83" of *Borrelia burgdorferi* might have been etiological guilty of acting as one of the eventual Hsps of the *Borrelia burgdorferi*. These probable pathogenetic associations had not been reported between generalized granuloma annulare and Lyme disease previously.

In the differential diagnosis, clinically, the granuloma annulare can be mistaken for other skin conditions, such as tinea, annular lichen planus, erythema annulare centrifugum, erythema chronicum migrans, erythema multiforme, tuberculides, sarcoidosis, tertiary syphilis and mycosis fungoides. Even though histopathology of the granuloma annulare is typical, sometimes it is confused with xanthoma, drug reaction, and rarely with *Mycobacterium marinum* infection.[17,21,22] In our case, the absence of foamy histiocytes, interface changes, and neutrophils and typical histopathologic features of the patient, allowed us to exclude those conditions from the diagnosis.

Oral doxycycline is the mainstay of therapy of cutaneous manifestations of borrelia infections.[1,45,46] We treated our patient, with oral doxycycline for 14 days (200 mg/day), because of the strong positive IgM antibodies that appear in the early phase of the Lyme disease.

Although "p83" is highly immunogenic polipeptide, we do not have any knowledge as to whether the "p83" is one of the Hsps of *Borrelia burgdorferi*, or not. As a result, to our knowledge, this case is the first reported generalized granuloma annulare associated with borrelia infection and "p83" in the literature. As our case is being reported to draw attention to this rare entity, a probable association of infection of borrelia with generalized granuloma annulare and its probable etiopathogenetic mechanism according to the concepts of the molecular mimicry and Hsps is being made. Unfortunately, so far there is not enough evidence to resolve the underlying causes of the pathogenesis of the granuloma annulare.

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