REVIEW

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Histopathological aspects in autoimmune cutaneous manifestations associated with hepatitis C virus infection

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Abstract

Autoimmunity is characterized by activation of the immune system that attacks and destroys wrongly, the body's own structures. All body tissues can be affected (erythrocytes, leukocytes, platelets, blood vessels, muscle tissue, endocrine system, and other), including the skin. Autoimmune diseases have an increased frequency in women, especially in adulthood, and they are associated with hereditary factors. Although the etiology of autoimmune diseases is incompletely elucidated, there is an association between chronic infection with hepatitis C and autoimmunity, association highlighted and well documented in clinical studies. Other viral infections do not have the same connotation in the context of autoimmunity, but it is recognized that they are an important triggering factor in the pathophysiological mechanism. The cases associating chronic hepatitis C treated with interferon and ribavirin, with multiple autoimmune diseases substrate, raising the discussion of a possible pathophysiological correlation between them.

Keywords: autoimmunity, chronic hepatitis C virus, interferon, ribavirin.

Introduction

The skin is a well-known reflection of our health status and many of the internal diseases are associated with skin manifestations [1].

This paper aims at raising the discussion of a possible pathophysiological correlation between chronic hepatitis C, treatment with interferon and ribavirin and multiple autoimmune diseases with cutaneous involvement. Hepatitis C is a common disease all over the world, so it should be recommended that, in carrying of the patient with hepatitis C to pay attention to the autoimmune manifestations and vice versa.

Autoimmune disorders and cutaneous manifestations

Autoimmune disorders, including lupus erythematosus, scleroderma, dermatomyositis, Sjögren's syndrome (SS), are relatively common diseases, but there are many diseases with unknown etiology, in which the autoimmune theory is discussed. Autoimmune cutaneous manifestations have a various range of clinical aspects, which can include also: livedo reticularis, psoriatic lesions, lichen planus lesions, lichen sclerosus, vitiligo, alopecia areata, or paraneoplastic disorders.

Autoimmunity is characterized by a break in the immune tolerance to self. The mechanism of this break is multifactorial, including genetic and environmental factors. From the list of environmental factors, infections and drugs are the most known and discussed [2].

Infections and autoimmune disorders

Infections have been suggested as a possible factor implicated in autoimmunity and the mechanisms involved can be: the modulation of the immune response by released inflammatory cytokines [*e.g.*, interferon-alpha (IFN-α) from antigen presenting cells (APCs)], molecular mimicry – the cross-reaction due to production of antibodies or T-cells that reacts with both autoantigens and foreign antigens, and the presence of superantigens, that induce a polyclonal activation of autoreactive T-cells [2]. This mechanism is not yet completely proven, but the association of viral infections, such as viral hepatitis C (VHC) and Epstein–Barr virus (EBV), with autoimmune manifestations is very frequent in clinical practice. The pathogenetic link between hepatitis C virus (HCV) and the immune system in inducing autoimmunity is still not completely understood. The mechanisms involved in this immune dysregulation are still unclear, but may be related with the lymphotrophic nature of the virus [3]. HCV may localize in different tissues (salivary glands, kidney, skin, etc.) in not only liver, contributing in both persistence and reactivation of the disease, but also playing an important role in the stimulation of the immune system, including the autoimmune mechanisms.

Drug-induced autoimmunity

Another discussion is connected with drug administration. Certain drugs can induce autoimmune diseases or manifestations (*e.g.*, procainamide, hydralazine, ribavirin, etc.), but, ironically, drugs that modulate the immune system, for example IFN-α, can also induce autoimmunity. The association between IFN-α treatment, for hepatitis C or malignancies, with drug-induced lupus, associated with nephritis, antineutrophil cytoplasmic antibodies-associated vasculitis, have been reported, and the involvement of

IFN-α in the pathogenesis of lupus erythematosus was suggested from late 1970s [2].

Studies in the field of autoimmune diseases show a higher combination of chronic hepatitis C infection with the various autoimmune diseases with clinical and histopathological manifestations, which may be located at different levels.

Some skin manifestations of autoimmune mechanism may be aggravated or induced by the therapy with interferon (lichen planus, vitiligo, and other).

Autoimmune diseases, cutaneous manifestations and chronic viral hepatitis C

Given the above, the presence of autoimmune diseases in a patient diagnosed with chronic hepatitis C virus requires reassessment of therapeutic management, balancing the positive effects with the adverse effects that may arise in evolution. Because of this, we will present the most common dermatological aspects of autoimmunity associated with chronic hepatitis C.

Literature describes the association of lichen planus with hepatitis C, as well as between antiviral treatment for hepatitis C and vitiligo, without giving definitive proof of the later [8].

Liver infection with hepatitis C, a member of the *Flaviviridae* family, is one of the well-documented associations with autoimmunity in skin diseases [4]. Chronic HCV infection is associated with the expansion of B-cell clones that may lead to autoimmunity. The phenotypic characterization of these B-cell clones (*e.g.*, CD20+ CD5+, CD5–CD20+ and CD5+BAFF+) has been reported [3]. Autoimmunity and extra-hepatic manifestations in hepatitis C infection are related to same impairment of the host Th1-immune response generation. Clinical studies have shown the presence of autoimmune diseases in 40–74% of patients with chronic hepatitis C, the percentage differences are related to regional variations [5, 6]. The hepatitis C virus can have extrahepatic locations, being detected in the kidney, blood vessels, blood cells, skin and salivary glands. Increased production of anti HCV antibodies is one of the bases of the autoimmune stimulation mechanisms; these patients can have other autoimmune features and antibodies, such as antinuclear antibodies (ANA) (41%), rheumatoid factor (38%), anticardiolipin antibodies (27%) or antithyroglobulin antibodies (13%) [4, 7].

From the hematological manifestation, immune thrombocytopenic purpura is common, the mechanisms discussed being linked to liver cirrhosis and hypersplenism associated with hypertension; production of antiplatelet autoantibodies and megakaryocytes due to their infection by hepatitis C; molecular mimicry mechanism between HCV and platelets glycoprotein can be the cause.

Rheumatological autoimmune diseases associated with HCV chronic infection can be Sjögren's syndrome, arthritis and fibromyalgia [8], over 60% of patients with HCV associated arthropathy were IgM rheumatoid factor positive. Differentiation between rheumatoid arthritis and rheumatoid arthritis-like in VHC is complex and sometimes difficult to perform. Arthritis of the VHC is symmetric, affects large joints, do not produce bone changes, no subcutaneous nodules and no inflammatory syndrome, citrulline or anti-keratin antibodies [9, 10]. Sjögren's syndrome is one of the most common association (over 250 cases reported) [4], with chronic HCV infection, being demonstrated the existence of viral replica in the salivary gland epithelial cells (there are genetic factors that can promote glandular destruction). Therefore, chronic hepatitis C may mimic the clinical features, histological and immunological changes of Sjögren's syndrome [11]; pathophysiological overproduction of autoantibodies are found as a result of hyperactivity and expansion of B-lymphocytes (Ly) and CD5+ B-Ly, producing polyreactive antibodies and rheumatoid factor [12]. Different mechanisms are discussed in connection with the pathogenesis of SS associated with HCV infection, including the molecular mimicry between the salivary gland and HCV, the formation of immune complexes associated with HCV [4].

Systemic lupus erythematosus is also associated with chronic HCV infection, the two diseases having in common immunological features as autoantibodies (anti-nuclear, anti-cardiolipin) and hypocomplementemia. In the same time, the immune complexes formed in the context of HCV infection can facilitate the development of lupus nephritis [4]. Kidney involvement associated with autoimmunity and HCV infection can be also represented by glomerulonephritis, membranous nephropathy, or IgA nephropathy [13].

Neurological involvement is discussed and represented by peripheral sensory neuropathy being by far the most common neurological manifestation, justified by identifying of viral RNA in peripheral nerves muscle, brain. Other changes described were: encephalomyelitis, myelitis, Guillain–Barré syndrome – by direct invasion or antibodies production [14, 15].

Autoimmune hepatitis, characterized by increased production of gamma-globulin, and good response to immunosuppressive autoantibodies, is common and are described two types of autoimmune hepatitis: type I, characterized by the presence of ANA, smooth muscle autoantibodies (SMA) and type II and characterized by anti-LKM1 (anti-liver–kidney microsomal) antibodies. In this context, hepatitis C is the trigger factor and the development of the disease occurs in genetically predisposed ground [16].

Dermatological manifestation can be the main target of autoimmunity in chronic hepatitis C [17], lichen planus being usually associated, but studies to date have not reached a consensus. Viral RNA was found in the skin, oral mucosa in patients with lichen planus, the combination is supported by *in vitro* hybridization studies [18]. Immune mechanisms involved in the association of HCV–oral lichen identification was suggested by viral sequences in oral mucosa affected, and the presence of CD4+ T-Ly and/or CD8+ HCV specific at this level. At the current time, the exact pathological way of action of HCV in the initiation and progression of the disease is not completely understood.

Vitiligo is another autoimmune cutaneous disease indicated by studies to date with similar rates of prevalence in patients with hepatitis C virus infection and in the healthy population with vitiligo [19].

Alopecia areata can also be associated, the role of hepatitis infection has not been revealed yet. Although

alopecia areata, with unknown association with infections, was observed frequently after interferon therapy for hepatitis C virus established [20].

Psoriasis is also discussed in connection with HCV infection because of the studies that found anti-HCV antibodies in psoriatic patients and HCV-RNA in the lesions of patients with psoriasis and HCV infection [4].

Autoimmune thyroiditis was the most discussed endocrinological diseases, described as one of the most problematic extrahepatic autoimmune diseases associated with hepatitis C, but studies show conflicting results in this area [21]. Pathogenic mechanism is based on two assumptions: direct cytopathic effect of the virus-induced autoimmunity secondary through molecular mimicry mechanism [22]. For these thyroid patients have suggested careful monitoring, especially before and after IFN therapy.

IDDM (insulin-dependent diabetes mellitus) is indicated by studies with increased susceptibility to contact HCV infection. There are influences inverse HCV infection affects progression to insulin-resistance is the best predictor for diabetes [23]. The connection is suggested by recent studies indicating remarkable structural similarities in the amino acids of HCV and GAD65 (glutamic acid decarboxylase), Ag2 islet cells (protein tyrosine phosphatase) and phogrin [24].

Autoimmune manifestations associated with chronic hepatitis C may be influenced by the treatment with interferon and ribavirin.

Therapy with interferon may be associated with immune-mediated skin lesions, causing their aggravation. Interferon therapy, associated with different regimens with ribavirin, can exacerbate dermatological manifestations and immunosupresor therapy for skin disorders may increase viral load and worsen liver disease.

IFN-α induce autoantibodies in more than half of patients treated for chronic hepatitis C. Common antibodies are anti-thyroid, anti-nuclear, antibodies against islets, in some patients can occur autoimmune features [25].

The systemic side effects might indicate that the Th17/interleukin (IL)-17 axis plays a prominent role in the immunopathogenesis of the autoimmune process, mainly in the psoriasiform lesions.

Studies carried out in patients with interferon therapy are conducted on small series of patients, the results are inconclusive but are described lesions suggestive of new or worsening systemic lupus erythematosus, dermatomyositis (they share common histological features and a similar gene expression signature with an overexpression of type I interferon-inducible genes), systemic sclerosis, vitiligo, lichen planus, even the occurrence of lesions post-therapy with interferon, in the absence of hepatitis C virus [26, 27].

The immunological cascade involved in the development of lesions of lichen planus contains proteins whose synthesis is controlled by interferon (IF187, IRF1, IFTM1, CXCL9) proteins that are increased in the lesions. Thus, interferon promotes accumulation and differentiation into Th1-Ly than followed by migration and adherence of keratinocytes and stimulate tissue toxicity [28].

Another association was suggested by the development of vitiligo lesions mechanism based on antibodies or activation of cytotoxic antimelanocytic T-Ly.

It is very important to put in balance the positive and negative effects of the immunomodulatory therapy, mainly in the cases of dermatologically patients with autoimmune-associated diseases.

Histopathological aspects can conclude the diagnosis, being one of the most important investigations in the cases of patients with autoimmune manifestations.

The biopsy from skin lesions can show, in lichen planus, uneven epidermis, epidermal thickening, liquefaction of the basal layer below which stands an abundant inflammatory infiltrate lymphomonocytary willing band with epithelial tropism and the slope area described inflammation comply epidermis compared which is separated collagen fibers – aspects suggest a lichen type lesion (Figure 1).

The result from genital lesions can describe changes characteristic for lichen sclerosus: epidermal atrophy, perivascular inflammation, dense papillary dermis with hyalinization (Figures 2–4). From the vitiligo lesions, the biopsy shows in Hematoxylin–Eosin (HE) staining a normal aspect, except for the absence of melanocytes (Figure 5).

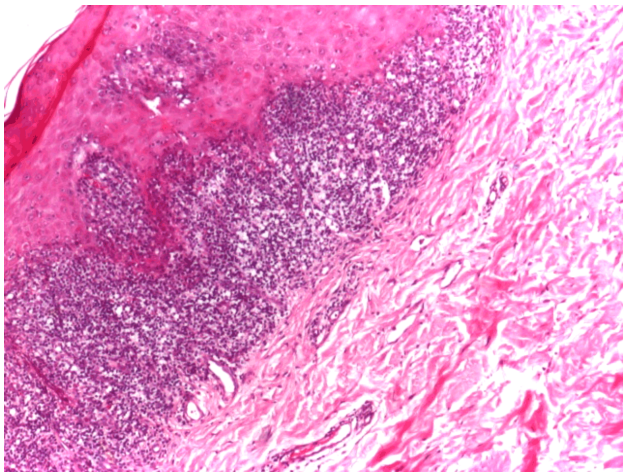

Figure 1 – ***Uneven epidermis epidermal thickening liquefaction. HE staining, ×40.***

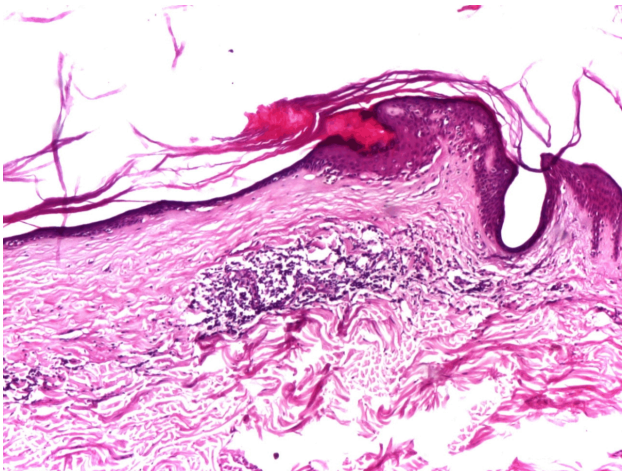

Figure 2 – ***Epidermal atrophy, perivascular inflammation, dense papillary dermis with hyalinization. HE staining, ×100.***

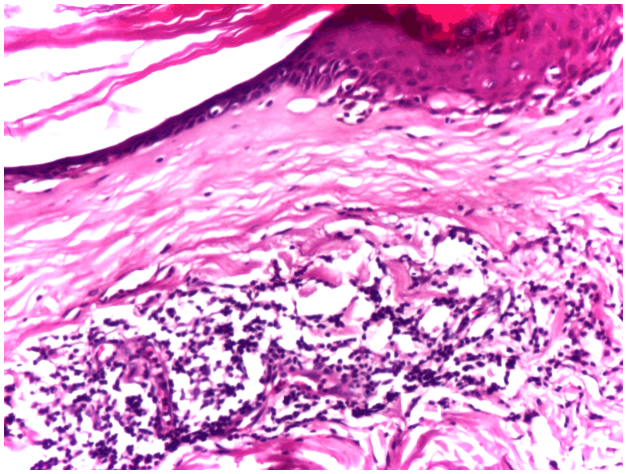

Figure 3 – ***Detail of previous figure. Epidermal atrophy, perivascular inflammation. HE staining, ×200.***

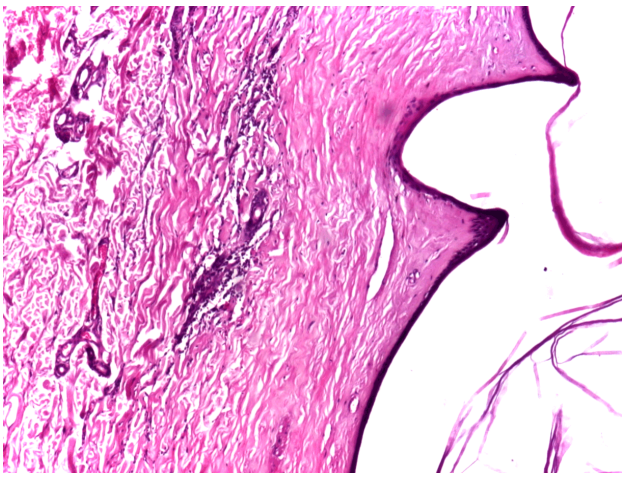

Figure 4 – ***Epidermal atrophy, perivascular inflammation, dense papillary dermis with hyalinization. HE staining, ×100.***

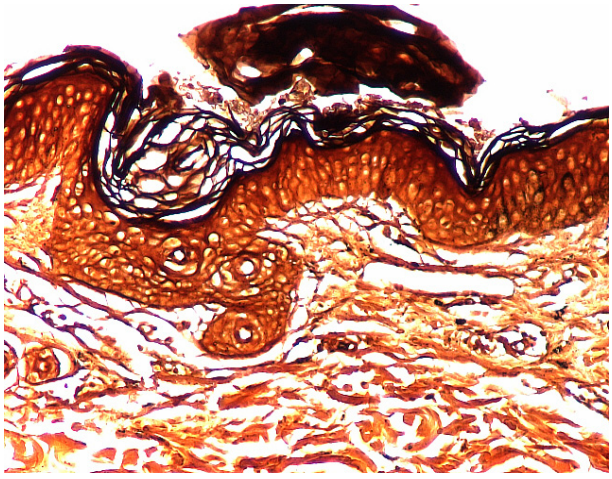

Figure 5 – ***Vitiligo absence of melanocytes. Fontana staining, ×100.***

Conclusions

The exact causes of autoimmune diseases are not known, but it is known and proven through numerous clinical studies that viruses are one of the important etiological factors/triggers in this mechanism. Hepatitis C virus is one with the most numerous cases of combination with autoimmune diseases, the severity of autoimmune diseases exceeding the severity of the hepatitis, making it mandatory to verify the association hepatitis C virus–autoimmunity. The pathophysiological mechanisms are not completely understood, but we know that the immune complexes, the molecular mimicry and the regulatory T-cells play an important role in autoimmune reaction associated with HCV.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Rashtak S, Pittelkow MR. Skin involvement in systemic autoimmune diseases. Curr Dir Autoimmun, 2008, 10:344–358.

[2] Kang I, Craft J. Mechanisms of autoimmune diseases. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ (eds). Fitzpatrick's dermatology in general medicine. 7th edition, McGraw–Hill Medical, 2008, 1509–1514.

[3] Böckle BC, Baltaci M, Ratzinger G, Graziadei I, Vogel W, Sepp NT. Hepatitis C and autoimmunity: a therapeutic challenge. J Intern Med, 2012, 271(1):104–106.

[4] Jadali Z, Alavian SM. Autoimmune diseases co-existing with hepatitis C virus infection. Iran J Allergy Asthma Immunol, 2010, 9(4):191–206.

[5] Doutre MS. Hepatitis C virus-related skin diseases. Arch Dermatol, 1999, 135(11):1401–1403.

[6] Lazaro P, Olalquiaga J, Bartolomé J, Ortiz-Movilla N, Rodríguez-Iñigo E, Pardo M, Lecona M, Pico M, Longo I, García-Morrás P, Carreño V. Detection of hepatitis C virus RNA and core protein in keratinocytes from patients with cutaneous lichen planus and chronic hepatitis C. J Invest Dermatol, 2002, 119(4):798–803.

[7] Ai J, Leonhardt JM, Heymann WR. Autoimmune thyroid diseases: etiology, pathogenesis, and dermatologic manifestations. J Am Acad Dermatol, 2003, 48(5):641–659; quiz 660–662.

[8] Tsuboi H, Yonemoto K, Katsuoka K. Vitiligo with inflammatory raised borders with hepatitis C virus infection. J Dermatol, 2006, 33(8):577–578.

[9] Simsek H, Savas C, Akkiz H, Telatar H. Interferon-induced vitiligo in a patient with chronic viral hepatitis C infection. Dermatology, 1996, 193(1):65–66.

[10] Chiorean R, Mahler M, Sitaru C. Molecular diagnosis of autoimmune skin diseases. Rom J Morphol Embryol, 2014, 55(3 Suppl):1019–1033.

[11] Ramos-Casals M, García-Carrasco M, Cervera R, Font J. Sjögren's syndrome and hepatitis C virus. Clin Rheumatol, 1999, 18(2):93–100.

[12] Curry MP, Golden-Mason L, Nolan N, Parfrey NA, Hegarty JE, O'Farrelly C. Expansion of peripheral blood CD5+ B cells is associated with mild disease in chronic hepatitis C virus infection. J Hepatol, 2000, 32(1):121–125.

[13] Kamar N, Izopet J, Alric L, Guilbeaud-Frugier C, Rostaing L. Hepatitis C virus-related kidney disease: an overview. Clin Nephrol, 2008, 69(3):149–160.

[14] Morgello S. The nervous system and hepatitis C virus. Semin Liver Dis, 2005, 25(1):118–121.

[15] Lacaille F, Zylberberg H, Hagège H, Roualdès B, Meyrignac C, Chousterman M, Girot R. Hepatitis C associated with Guillain–Barré syndrome. Liver, 1998, 18(1):49–51.

[16] Pavić S, Simonović J, Boricić I, Svirtlih N. [Autoantibodies characteristic for autoimmune hepatitis found in chronic hepatitis C]. Srp Arh Celok Lek, 2003, 131(11–12):437–442.

[17] Nocente R, Ceccanti M, Bertazzoni G, Cammarota G, Silveri NG, Gasbarrini G. HCV infection and extrahepatic manifestations. Hepatogastroenterology, 2003, 50(52):1149–1154.

[18] Arrieta JJ, Rodriguez-Inigo E, Casqueiro M, Bartolomé J, Manzarbeitia F, Herrero M, Pardo M, Carreno V. Detection of hepatitis C virus replication by *in situ* hybridization in

epithelial cells of anti-hepatitis C virus-positive patients with and without oral lichen planus. Hepatology, 2000, 32(1):97–103.
[19] Jadali Z, Eslami MB, Sanati MH, Mansouri P, Mahmoudi M, Maghsoudi N, Esfahanian F. Hepatitis C virus antibodies and vitiligo disease. Iran J Publ Health, 2005, 34(1):23–26.
[20] Jadali Z, Mansouri P, Jadali F. There is no relationship between hepatitis C virus and alopecia areata. Eur J Dermatol, 2006, 16(1):94–95.
[21] Jadali Z, Esfahanian F, Eslami MB, Sanati MH. Serum antibodies against hepatitis C virus in Iranian patients with Graves' disease. Iran J Allergy Asthma Immunol, 2005, 4(2): 91–94.
[22] Piszko P, Fleischer K, Simon K, Serafińska S. [Endocrine disorders in HCV infection]. Przegl Epidemiol, 2006, 60(4): 707–714.
[23] Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, McCaughan GW, George J. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. Gastroenterology, 2003, 125(6):1695–1704.
[24] Bogdanos DP, Rigopoulou EI. Viral/self-mimicry and immunological cross-reactivity as a trigger of hepatic C virus associated autoimmune diabetes. Diabetes Res Clin Pract, 2007, 77(1):155–156.
[25] Kolb-Mäurer A, Goebeler M, Mäurer M. Cutaneous adverse events associated with interferon-β treatment of multiple sclerosis. Int J Mol Sci, 2015, 16(7):14951–14960.
[26] Jadali Z. Dermatologic manifestations of hepatitis C infection and the effect of interferon therapy: a literature review. Arch Iran Med, 2012, 15(1):43–48.
[27] Vergani D, Mieli-Vergani G Autoimmune manifestations in viral hepatitis. Semin Immunopathol, 2013, 35(1):73–85.
[28] Marrack P, Kappler J, Mitchell T. Type I interferons keep activated T cells alive. J Exp Med, 1999, 189(3):521–530.

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