Case Report

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Hepatitis C and cutaneous alterations

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ABSTRACT

While most of those infected with hepatitis C virus (HCV) are asymptomatic or only develop liver manifestations, a significant percentage evolves with autoimmune and lymphoproliferative disorders, resulting in a clinical condition called HCV syndrome. This work involving case studies of six patients with hepatitis C and varied skin manifestation aimed to report skin lesions occurring with HCV infection and its treatment. Skin manifestations in hepatitis C have been based on epidemiological studies. This justifies the need for studies that correlate HCV infection and its treatment with skin manifestations.

Keywords: Autoimmune disorders. Hepatitis C virus. Skin.

INTRODUCTION

The World Health Organization estimates that about 170 million people are infected with hepatitis C virus (HCV) worldwide[1]. This virus has been considered a global public health problem, because of its high prevalence and liver and extrahepatic manifestations[2,3].

About 85% of infected individuals progress to chronicity. Besides evolving slowly for years or decades, chronic infection with HCV often presents a wide clinical spectrum from asymptomatic with normal enzymes to severely active chronic hepatitis, which is why a strong effort has been made to achieve early diagnosis[4].

The most frequent skin manifestations are vasculitis associated with cryoglobulinemia, lichen planus, porphyria cutanea tarda, necrolytic acral erythema, erythema multiforme, erythema nodosum, pruritus and psoriasis[5,6].

In recent years, several studies have shown that liver lesions are related to immune-mediated mechanisms. The quality of the cell-mediated immune response is crucial for the elimination or persistence of HCV, according to the most widely accepted current hypothesis. TCD4 lymphocytes present distinct Th1 and Th2 responses; while Th1 cells secrete interleukin 2 (IL-2) and interferon-gamma stimulating a host anti-viral response, Th2 cells produce IL-4 and IL-10, which stimulate antibody formation and inhibit the Th1 response. An imbalance between the Th1 and Th2 responses could be responsible for both the inability to eliminate HCV and the degree of severity of the liver lesions. However, the elements that influence the development of one or other type of immune response remain unknown.

Concerning the skin, the manifestations of HCV can originate from three actions of the virus. Direct action is caused by the presence of viral particles in keratinocytes, lymphocytes, antigen presenting dendritic cells and blood vessels. Indirect action occurs as an epiphenomenon secondary to dermal immune disorders, such as the formation of immune complexes or autoimmune processes. The third viral action derives from the functional impairment of other organs and consists of cutaneous manifestations of the affected organ, though not related to the virus[7].

The association of interferon-alfa (IFN-α) with ribavirin enhances sustained viral response to 38 to 43%, with corresponding improvement in the histological analysis (biopsy) and possibly in the long-term complications of hepatitis; however, data for the latter lacks long-term prospective studies.

Interferons are a group of glycoproteins involved in the regulation of antiviral and antiproliferative responses of the autoimmune system. Interferon-alpha acts directly against the virus and increases the immune response; however, treatment with IFN-α alone only presents 10 to 19% sustained response. The immunomodulatory effects of INF-α induce aberrant behavior in inappropriately stimulated T lymphocytes and result in abnormal reactions to normal stimuli.

Ribavirin is a synthetic analogue of guanosine that acts directly against virus ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), probably through a mechanism of virus-dependent DNA polymerase inhibition. However, ribavirin alone has no effect on hepatitis C. The principal side effect of the use of ribavirin is the induction of hemolysis, which occurs in almost all patients. However, it is usually well tolerated, since it is mild and reversible following suspension of the medication.

The association of pegylated interferon with ribavirin for the treatment of chronic hepatitis C may be responsible for several types of skin lesions, including local reactions at the application of interferon and other diseases, such as psoriasis, lichen planus, vitiligo and systemic lupus erythematosus[8]. The combination probably induces a higher incidence of cutaneous adverse effects compared to the use of interferon alone, though ribavirin alone only rarely causes photosensitivity.

Skin manifestations in hepatitis C are usually based on epidemiological studies. No further evidence of this association is available, nor have such studies defined how HCV acts in determining these diseases[9].

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This work involving case studies of six patients with hepatitis C and varied skin manifestations aimed to report the skin lesions occurring with HCV infection and its treatment.

CASES REPORTS

Hepatitis and psoriasis

Identification: E.D.B., 53 years-old, male, white, retired, born in Conquista, MG, resident of Igarapava, State of São Paulo, Brazil; chief complaint and duration (CCD): spots on his face for two months; history of present illness (HPI): the patient reported the appearance of symmetrical, achromatic spots, with irregular edges, on the forehead and malar region of the face, two months prior to attendance. He also reported erythematous, scaly lesions on the scalp and further stated that the lesions began 10 months following the onset of treatment with interferon and ribavirin for hepatitis C; past medical history (PMH): hemophilia A, diabetes mellitus type 2, hypertension; complementary information (CI): 2 blood transfusions; dermatological exam: irregular achromatic spots measuring 6x4cm on the forehead and 6cm in diameter in the malar region. The presence of erythematous, scaly lesions was observed on the scalp; diagnostic hypothesis (DH): widespread psoriasis plaques, skin biopsy not possible due to prior hemophilia A; recommended treatment (RT): 0.1% tacrolimus was prescribed for the achromatic facial lesions and 0.05% clobetasol propionate lotion for the scalp lesions; therapeutic outcome (TO): patient follow-up at 4 months showed improvement of achromatic lesions on the face, though erythematous papules were observed on the abdomen and erythematous, scaly plaques in the sacral region and on the elbows, knees and thighs. On 10/02/2009 we prescribed subcutaneous administration of 50mg of etanercept per week. After 8 weeks, the patient presented improvement in almost all the lesions.

Hepatitis and vitiligo

Identification: L.E., 58 years-old, male, white, married, painter, born in Barretos, State of São Paulo, resident of Uberaba, State of Minas Gerais, Brazil; CCD: spots on his body for at least a year; HPI: the patient reported the appearance of diffuse, achromatic spots throughout the body, for at least a year. He denied emotional disturbances. He showed weight loss of 10kg in 1 year. Four months previously, he had been diagnosed with chronic hepatitis C, but did not initiate treatment; PMH: hepatitis A in childhood, smoker (marijuana), former illicit drug user (including injectables), alcoholic for 30 years; CI: two tattoos in the preceding 10 years; dermatological exam: achromatic spots, with areas of pigmentation, diffuse throughout the body, particularly the face, arms and trunk; RT: treatment with betaderm was prescribed (1 per night); On 19/01/2009 a programmed liver biopsy was not performed due to thrombocytopenia. On 16/02/2009 we programmed onset of hepatitis C treatment. We also orient the patient to stop alcoholism.

Hepatitis and vitiligo

Identification: E.A.S., 55 years-old, male, white, single, traveler, born in Santos, State of São Paulo, and resident in Uberaba, State of Minas Gerais, Brazil; CCD: white spots on his face for two months; HPI: the patient reported the appearance of achromatic and hypochromic spots on his face, with irregular edges, some measuring 5x2cm, especially in the forehead and malar region, which was diagnosed as vitiligo. The appearance of these lesions (08/07/2008) occurred 6 months after initiating treatment for hepatitis C (25/01/2008) with IFN-α and ribavirin. The patient also reported depressive mood and emotional lability during this period; PMH: former injectable drug user; *exams*: serology (18/12/2006): anti-HBC reagent; RT: treatment with 0.1% tacrolimus (26/11/2008) was prescribed for 5 months, with minimal therapeutic response. *Brosimum gaudichaudii* Trécul in association with betamethasone (23/04/2009) was then prescribed and resulted in good therapeutic response.

Hepatitis and chronic discoid lupus

Identification: S.O., 47 years-old, female, white, married, born in and resident of Uberaba, State of Minas Gerais, Brazil; CCD: spots for around 6 months; HPI: the patient reported the appearance of bilaterally symmetrical, red spots on her neck and reddish plaques in areas exposed to sunlight, which progressed with painful, burning and itching sensations, that appeared one day following the application of IFN-α. After 10 weeks, the lesions evolved to hypochromic, scaly plaques on her neck, back, shoulders, arms, scalp and lower eyelids. At week 41, a palpable posterior cervical lymph node was observed on the left side and the spots presented a lamellar aspect. At week 48, the patient presented hyperchromic maculae on her face (right periorbital region), neck and shoulders, which worsen following sun exposure, as well as lichenified plaques on the neck and back; PMH: asymptomatic carrier of hepatitis C, which had been treated with IFN-α and ribavirin 21 weeks previously; *Histopathology*: the lesions were biopsied, which revealed dermatitis of the lichenoid and vacuolar interface compatible with chronic discoid lupus; TO: treatment with 0.05% clobetasol propionate cream and sunscreen was prescribed, resulting in regression of the lesions.

DISCUSSION

Skin manifestations related to HCV infection can be caused by the three distinct viral actions. Direct action occurs in keratinocytes, lymphocytes, antigen presenting dendritic cells and blood vessels. Indirect action is due viral action, involving the formation of immune complexes or autoimmune processes. The third possibility is viral action derived from the functional impairment of other organs, which consists of cutaneous manifestations of the affected organ not directly related to the virus.

The diagnosis of skin diseases that could be cutaneous manifestations of HCV infection indicates the need to submit the patient to investigation aimed at providing early detection and diagnosis.

Vitiligo

Vitiligo is a relatively frequently acquired leucoderma that affects about 1% of the population. In 30% of cases, familial occurrence is observed. Occasionally, vitiligo occurs after trauma or sunburn.

The autoimmune response is considered a significant component in the pathogenesis of vitiligo. An association between vitiligo and IFN-α therapy has been reported and it is possible that IFN-α induces anti-melanocyte antibodies or cytotoxic T cell activation. In addition, the potential involvement of hepatitis C virus in autoimmune vitiligo has been suggested. Another possibility is that vitiligo occurs due to a neuropsychological mechanism induced by IFN-α.

Psoriasis

Psoriasis is classified as an immune-mediated, chronic inflammatory disease, since it results from the concomitant dysregulation of T lymphocytes with consequent changes in the metabolism of keratinocytes[10]. It is characterized by relatively frequent, erythematous, scaly lesions that affect up to 1% of individuals in certain populational groups. It occurs equally in both sexes and can occur at any age.

Etiopathogenesis: the cause of the disease is unknown, though predisposition to the disease is genetically determined. Several factors have been implicated in the onset or exacerbation of psoriasis: cutaneous trauma of various kinds, infections, drugs, emotional stress and others, including endocrine and metabolic disorders, increased alcohol intake and climatic variation.

The pathogenesis of psoriasis presents shortening of the epidermal germinative cycle, increased cell proliferation and marked shortening of the period of cell turnover of the epidermis of psoriatic lesions.

Few studies have been conducted to improve current understanding regarding the relation between psoriasis and HCV. Among those published, the results are contradictory, although none exclude the plausibility of the existing hypothesis[11], such that they recommend detailed dermatological examination should be performed on all patients with positive immunological tests for HCV and such tests are ordered for patients with a confirmed diagnosis of psoriasis.

Early investigations sought to determine the prevalence of HCV in patients with psoriasis, especially following the use of INF-α in the treatment of chronic hepatitis by this virus.

Certain studies have already attempted to demonstrate the benefits of studying the association between psoriasis and HCV infection, which could lead to more appropriate therapy. Given that the therapeutic use of systemic therapy for psoriasis consists of hepatotoxic drugs, the drugs used to treat HCV infection may exacerbate psoriasis. Thus, in patients presenting an association of these diseases, choosing the most cost effective regimen is an option.

Chronic discoid lupus

A dermatosis that shows chronic evolution that is probably triggered by an autoimmune process and constitutes the most common clinical variant of lupus erythematosus. Disease occurrence is universal among all races, is more common in women over 40 years of age and is rare in children. The skin lesions are caused or aggravated by exposure to ultraviolet radiation, cold and drugs and present chronic, insidious evolution.

Clinical manifestations: discoid lesions are characterized by pink to purple erythema, with central atrophy and desquamation, which frequently affect the face, especially the cheeks and the nose, acquiring a butterfly wing aspect. Other affected locations include: the ears, lips, scalp and oral mucosa. It affects the scalp areas, where the lesions cause alopecia. The chronic forms show central atrophy that often results in scarring. In late stages, residual hyperpigmentation and telangiectasia can occur.

Hepatitis C

Hepatitis C is liver inflammation caused by infection with the hepatitis C virus, transmitted through contact with contaminated blood. This inflammation occurs in most people who acquire the virus and, depending on the intensity and duration, can lead to cirrhosis and liver cancer. Unlike other viruses that cause hepatitis, HCV does not generate an adequate immune response in the organism, such that the resulting acute infection is less symptomatic and most people who are infected become carriers of chronic hepatitis, with long-term consequences.

Transmission: hepatitis C occurs after contact with infected blood. Recent reports have verified the presence of the virus in other secretions (milk, saliva, urine and semen). Hepatitis C virus can survive from 16 hours to 4 days in external environments. Higher risk groups include blood recipients, intravenous drug users, hemodialysis patients and healthcare workers.

Physiopathology: hepatitis C is caused by an RNA-type virus. Several genotypes (variants) of this virus exist, the most important of which is 6 (1 to 6), and these are subdivided into more than 50 subtypes (1a, 1b, 2a, etc.). The genotypes can present from 30 to 50% difference in their RNA. This division is important because each subtype has its own characteristics of aggressiveness and response to treatment. Genotypes 1 and 4 present greater resistance to interferon treatment than 2 and 3. The variants can *trick* the immune system and greatly hinder the production of vaccines, among other complications. Similar to hepatitis B infection, current data suggest that the main mechanism of liver cell destruction occurs through attacks by the host immune system, though it is likely that destruction is also caused by the virus.

Diagnosis: the primary diagnostic method for hepatitis C remains anti-HCV serology by enzyme-linked immunosorbent assay (ELISA). Given the high reliability of the exam, use of serology by another method such as recombinant immunoblot assay (RIBA) should only be considered when a false positive by ELISA is suspected, such as individuals with no risk factors. A false positive result is more common among patients presenting autoimmune diseases and individuals who have had acute hepatitis C that healed spontaneously, but who retain positive serology for several weeks. Several methods can be used: qualitative polymerase chain reaction (PCR) is more sensitive and detects even minute amounts of viral RNA, 50 copies/mL; while quantitative PCR is less sensitive, only above 1,000 copies/mL, but provides a good estimate the amount of circulating virus. Determining the genotype is unnecessary to diagnose the infection, but it is extremely important in making treatment decisions; genotypes 2 and 3, for example, require smaller medication doses and less treatment time than those recommended for genotype 1.

The skin manifestations of HCV infection indicate a need to submit the patient to a thorough investigation that permits early diagnosis. Knowledge of extrahepatic manifestations facilitates the diagnosis, since these may be more pronounced than the clinical status of the liver in the initial phase of infection.

Cutaneous manifestations are frequently associated with cryoglobulinemia vasculitis, lichen planus, porphyria cutanea tarda, necrolytic acral erythema, erythema multiforme, erythema nodosum, pruritus and psoriasis.

The use of pegylated interferon in patients with hepatitis C can be associated with a variety of adverse effects, including its immunomodulatory properties, which are capable of inducing autoimmune phenomena, particularly in predisposed patients. The

association of pegylated interferon and ribavirin in the treatment of chronic hepatitis C could be responsible for several types of skin lesions: reactions at the application site, psoriasis, lichen planus, vitiligo and systemic lupus erythematosus. The incidence of skin reactions in this combined treatment remains unknown, though it could well be higher than currently estimated and is related to the greater incidence of cutaneous adverse effects, compared to the use of interferon alone. The use of ribavirin alone only appears to cause photosensitivity.

Numerous skin diseases, if not the majority, are directly related to autoimmune mechanisms, such as vitiligo and psoriasis. It is known that the autoimmune response is a significant component in the pathogenesis of vitiligo. An association between vitiligo and IFN-α therapy has previously been reported. Furthermore, it has been suggested that the hepatitis C virus itself is involved in autoimmune vitiligo. Studies have attempted to show the association between psoriasis and HCV infection and that the drugs used in treatment of viral infections can exacerbate psoriasis.

In conclusion, both the treatment for HCV infection and the virus could be associated with cutaneous compromise (mostly autoimmune) in these patients, which justifies the need for studies that correlate HCV infection and its treatment with the skin manifestations that occur.

ABSTRACT IN PORTUGUESE

Hepatite C e alterações cutâneas

A maioria dos infectados pelo vírus da hepatite C (VHC) é assintomática ou apresenta somente manifestações hepáticas, porém uma significativa porcentagem evolui com desordens autoimunes e linfoproliferativas resultando na síndrome da hepatite C. Este trabalho envolve seis estudos de casos de pacientes com hepatite C e várias manifestações cutâneas, visando relacionar lesões dermatológicas ao VHC e ao seu tratamento. Manifestações dermatológicas na hepatite C têm sido baseadas em estudos epidemiológicos. Isto justifica a necessidade de estudos que correlacionem infecção pelo VHC e seu tratamento com as manifestações dermatológicas.

Palavras-chaves: Desordens autoimune. Vírus da hepatite C. Pele.

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