ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LX, N 1, 50 SECTIO D 2005

Department of Infectious Diseases, Medical University of Lublin

KRZYSZTOF TOMASIEWICZ, ROMA MODRZEWSKA, ANNA ŁYCZAK, IRENA BOROWICZ

Dermatologic manifestations in hepatitis C virus (HCV) infected patients – any etiopathogenic links?

Chronic hepatitis of hepatitis C virus (HCV) etiology is one of the most important global public health problems. A global prevalence of HCV infection is thought to exceed 3% of general population that is more than 170 million individuals all over the world. Many of them are at risk for liver cirrhosis and hepatocellular carcinoma development. HCV became one of the most important carcinogens and in spite of introduction of modern antiviral treatment with α-interferon and ribavirin, the prognosis for a significant number of patients is rather poor (7).

Besides liver problems the virus may be responsible for a wide spectrum of extrahepatic manifestations. They include endocrine and hematological disorders, kidney and joints involvement, as well as autoimmune syndromes. Cutaneous manifestations constitute a significant part of extrahepatic abnormalities. There are at least two possible explanations for pathogenesis of these disorders. Viral infection is thought to trigger autoimmune processes, which may lead to several dermatological manifestations, particularly in individuals with some genetic predisposition. On the other hand in some cutaneous disorders replication of HCV was found in skin lesion, and direct tissue invasion by the virus should be considered. However, most of cutaneous manifestations seem to be immune mediated as the consequence of monoclonal and polyclonal lymphocyte reaction (7, 15).

Dermatolological disorders found in HCV infected patients may be divided into three groups. The first one contains often associated diseases, including mixed cryoglobulinemia, porphyria cutanea tarda, leukocytoclastic vasculitis and livedo reticularis. Less often associated disorders are lichen planus, Sjögren's syndrome, urticaria, pruritus and polyarteritis nodosa. In the last group uncommonly found manifestation are classified, including erythema nodosum, erythema multiforme, vitiligo, psoriasis, pyoderma gangrenosum, Behçet's syndrome, Mooren corneal ulcer, granuloma anulare and disseminated superficial actinic porokeratosis (8, 15).

In this paper we present highly prevalent skin diseases associated with HCV infection that may become the common problem for both dermatologists and infectiologists.

SKIN DISEASES IN HCV-POSITIVE PATIENTS

Mixed cryoglobulinemia

Mixed cryoglobulinemia is one of the most common skin manifestations in patients with chronic HCV infection. The aetiopathogenetic link between HCV and mixed cryoglobulinemia was suggested by epidemiological data. But it was firmly established using modern sensitive PCR technology. HCV-RNA sequences were identified both in cryoprecipitate and in purpuric skin lesions in much higher (100-1000-fold) concentrations compared to serum (12). In the cutaneous vasculitic lesions HCV was associated both with IgM and IgG antibodies, which was demonstrated

by immunohistochemical or *in situ* hybridisation techniques. Serum immune complexes precipitate at cold temperatures (7).

Mixed cryoglobulinemia is probably the consequence of the chronic stimulation of the immune system. Immune complexes activating endothelial cells increase vascular permeability and vessel wall damage is observed. Clinically it leads to variable symptoms of systemic vasculitis (12). The frequency of mixed cryoglobulinemia in patients with HCV infection is quite high. According to many published reports it is higher than 40%. Cryoglobulinemia is often observed in individuals with long history of chronic hepatitis C and in cirrhotic patients. The therapy with α-interferon leads to resolution of the skin manifestations and unsuccessful treatment of chronic hepatitis C may cause also relapses of mixed cryoglobulinemia (7, 15).

It is wise to screen for HCV infection every patient with cryoglobulinemia. Recently, possible malignant transformation of HCV related mixed cryoglobulinemia has been suggested (7).

Porphyria cutanea tarda

Porphyria cutanea tarda is described as a classic skin manifestation of HCV infection. However, HCV-RNA is found in 62% to 100% of patients with porphyria cutanea tarda. The study in Japan and several Mediterranean countries has shown the prevalence of anti-HCV or/and HCV-RNA in great part of patients with porphyria, suggesting a strong association (7, 18). On the other hand, Navas et al. has isolated HCV-RNA in liver sample and peripheral blood mononuclear cells of all patients with PCT, whereas it was found in serum in only 45% of cases (16). Interesting results of study conducted by Chiaverini et al. may suggest the genetic background for porphyria cutanea tarda development. They have found a statistically significant increase in the C282Y mutation of hemochromatosis gene, compared to no difference in H63D and S65C mutations (4). It is possible that gene might be additional triggering factor.

The reduction of hepatic uroporphyrinogen decarboxylase activity plays the key role in porphyria cutanea tarda pathogenesis. The concentration of porphyrins in the skin is the direct reason for phototoxic reaction and finally for increased collagen synthesis, which may result in sclerodermoid lesions. Clinical symptoms include increased skin fragility, vesicles, bullae and erosions that heal with scarring. They are present primary on sun-exposed skin surface (15).

The probable etiopathogenetic link between porphyria cutanea tarda and HCV infection may help to explain cases of hepatocellular carcinoma in porphyria patients. They might have been linked to HCV infection.

Discussing treatment strategy interferon-based therapy should be considered, although there are not many reports concerning efficacy of such therapy.

Lichen planus

Even more questions have arisen around the role of HCV in the development of lichen planus. Because it is quite common dermatological disorder the coexistence of lichen planus and HCV infection should be interpreted very cautiously. First reports of co-occurrence in individual patients were published in 1991 and did not let to draw firm conclusions (7). In 1995 Bellman et al. have published in Lancet the letter suggesting the association of lichen planus with chronic hepatitis C (1). Since that time several studies were done and the prevalence of anti-HCV in lichen planus patients ranged from 10% to 23% (7). Moreover, Kurokawa et al. have recently shown the presence of anti-genomic and genomic-strand HCV-RNAs in lichen planus lesions, which may suggest that HCV-associated LP lesions are sites of virus replication (11). On the other hand, Carrozo et al., analyzing Italian patients with HCV associated oral lichen planus, has demonstrated increased frequency of HLA-DR6 allele (3). No relation between the different genotypes of HCV and the presence of lichen planus lesions has been proved (17). Another interesting etiopathogenic implication is observation concerning the presence in keratinocytes of common epitopes similar to that of hepatocytes damaged by HCV. It is also hypothesized that HCV induce autoantibodies against the product of a host gene termed GOR. This protein shares several amino acids with the core gene product of HCV (15).

Taking the presented data and hypothesis all together, it is assumed that HCV may trigger lichen planus in genetically susceptible individuals. However, the treatment with α-interferon may more often deteriorate skin lesions than improve them. Even though, there are some reports of lichen planus eruption in the course of interferon treatment (7).

Nodular vasculitis

The essential pathology in nodular vasculitis is a lobular panniculitis associated with vasculitis of the septal blood vessels. Skin lesions are seen primary on the legs and include nodular, erythematous and painful ones, which may ulcerate and heal with scarring. There is no firmly established etiopathogenetic mechanism that could explain the development of skin damage.

The attractive hypothesis is the triggering of immune-mediated response by an infectious agent, including HCV. The possible initial point might be the local deposition of circulating immune complexes of antibodies against some HCV antigens and subsequent delayed immune hypersensitivity. The important argument for the role of HCV in nodular vasculitis is improvement of skin lesions after α-interferon therapy, that correlate with response of chronic hepatitis C (2).

Porokeratosis

The association of porokeratosis with immunosupresion and autoimmune diseases was reported in several papers. Characteristic skin lesions were observed in patients with leukaemia, myelodysplastic syndrome, human immunodeficiency virus (HIV) infection, as well as in individuals treated with systemic corticosteroids and receiving chemotherapy due to either autoimmune diseases or malignant neoplasm. In 1999, Mizukawa et al have reported three cases of porokeratosis associated with HCV infection. However it is difficult to establish the strong relationship between these two diseases, the virus might be treated as an exogenous factor, which interact with genetic ones. Probably, some of immunological dysfunction could trigger porokeratosis in genetically predisposed patients (14).

Urticaria

Urticaria is classically considered to be a symptom of hepatitis A (HAV) and hepatitis B virus (HBV) infection. In the early 90s the possible association with HCV was suggested (5). Such relationship was supported by Kanazawa et al., who have found 24% prevalence of HCV infection markers in the group of Japanese patients with urticaria (9). However, in several European studies, the rate of HCV infection was extremely low and did not exceed this observed in general population (5). Evaluation of patients presenting with urticaria should include the careful analysis of many possible etiopathogenetic factors, like food and drink changes, new medications and exposure to various chemicals. As the problem remains controversial, further studies are needed.

Behçet's disease

The etiology of Behçet's disease is still unknown. Since the disease was described in 1937, many etiopatogenic theories have been concerned. Among possible factors a special interest is aroused in infectious, particularly viral, agents. Because circulating immunocomplexes might be partly responsible for clinical symptoms of Behçet's disease, several large study screening for HCV infection markers, were conducted. Results of most of them have not shown any significant difference, when compared with healthy controls. It is thought the association of Behçet's disease and HCV is fortuitous (6).

Pyoderma gangrenosum

The association of pyoderma gangrenosum and chronic liver diseases has been frequently reported. However, only a few cases of pyoderma gangrenosum has been described in patients infected with HCV. Such coexistence may be underdiagnosed. The pathogenesis of skin lesions in pyoderma gangrenosum is still not clear. The abnormal lymphocyte function, perivascular immunoglobulin and complement deposition and circulating antibodies have been documented (10). As HCV can induce autoantibodies, it may play a role of triggering factor, but further observations are needed.

Skin B-cell lymphomas

Since *Borrelia* sp. were identified as a causative agent of some form of B-cell lymphoproliferative disorders of the skin, some etiopathogenic links between lymphomas and viral infection were suspected. Prevalence rates of HCV infection between 7 and 37% were reported in patients with B-cell non-Hodgkin lymphomas. Michaelis et al. have recently published the results of virological studies done in the group of 23 patients with various forms of cutaneous B-cell lymphomas. Using reverse transcriptase chain reaction (RT-PCR), they found HCV-RNA sequences in 30% of examined skin biopsies (13). These results and well-known ability of HCV to infect B-cells may suggest a possible pathogenetic link (7, 13). There are not many observations concerning the influence of α-interferon treatment on resolution/worsening of skin lesions in HCV infected patients. The remission of lymphoma would be an interesting argument for the possible role of HCV in B-cell skin lymphomas development (18).

The role of HCV in other, mentioned in the introduction, skin disorders remains unclear. The controversial results of studies undertaken in patients with polyarteritis nodosa, erythema multiforme or erythema nodosum, for example, have been published. There is one common conclusion that further studies are necessary to confirm or deny any etiopathogenetic links.

REFERENCES

1. Bellman B. et al.: Lichen planus associated with hepatitis. Lancet, 346, 1234, 1995.
2. Cardinali C. et al.: Hepatitis C virus: a common triggering factor for both nodular vasculitis and Sjögren's syndrome? Br. J. Dermatol., 142, 187, 2000.
3. Carrozo M. et al.: Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. Br. J. Dermatol., 144, 803, 2001.
4. Chiaverini C et al.: Porphyria cutanea tarda, C282Y, H63D and S65C HFE gene mutations and hepatitis C infection: a study from southern France. Dermatology, 206, 212, 2003.
5. Cribier B.J. et al.: Chronic urticaria is not significantly associated with hepatitis C or hepatitis G infection: A case-control study. Arch. Dermatol., 135, 1335, 1999.
6. Franco R.C.: Behçet's disease and HCV infection. Int. J. Dermatol., 39, 396, 2000.
7. Hadziyannis S.J.: Skin diseases associated with hepatitis C virus infection. J. Eur. Acad. Dermatol. Venereol., 10, 12, 1998.
8. Jackson J.M.: Hepatitis C and the skin. Dermatol. Clin., 20, 237, 2002.
9. Kanazawa K et al.: Hepatitis C virus infection in patients with urticaria. J. Am. Acad. Dermatol., 35, 195, 1996.
10. Keane F.M. et al.: Pyoderma gangrenosum and hepatitis C virus infection. Br. J. Dermatol., 139, 924, 1998.
11. Kurokawa M et al.: Analysis of hepatitis C virus (HCV) RNA in the lesions of lichen planus in patients with chronic hepatitis C: detection of anti-genomic- as well as genomic-strand HCV RNAs in lichen planus lesions. J. Dermatol. Sci., 32, 65, 2003.
12. Lunel F: Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. Gastroenterology, 106, 1291, 1994.

13. Michaelis S. et al.: Hepatitis C and G viruses in B-cell lymphomas of the skin. J. Cutan. Pathol., 369, 30, 2003.
14. Mizukawa Y., Shiohara T.: Porokeratosis in patients with hepatitis C virus infection: does hepatitis C virus infection provide a link between porokeratosis and immunosuppression? Br. J. Dermatol., 141, 163, 1999.
15. Matičič M: Hepatitis C virus infection: the dermatological perspective. Acta Dermatoven APA, 12, 19, 2003.
16. Navas S. et al.: Porphyria cutanea tarda and hepatitis C and B viruses infection: a retrospective study. Hepatology, 21, 279, 1995.
17. Sanchez Perez J. et al.: Lichen planus and hepatitis C virus infection: a clinical and virological study. Acta Derm. Venereol., 78, 305, 1998.
18. Tsukazaki N. et al.: Porphyria cutanea tarda and hepatitis C virus infection. Br. J. Dermatol., 138, 1015, 1998.

SUMMARY

Chronic hepatitis of hepatitis C virus (HCV) etiology is one of the most important global public health problems. A global prevalence of HCV infection is thought to exceed 3% of general population that is more than 170 million individuals all over the world. Besides liver problems the virus may be responsible for a wide spectrum of extrahepatic manifestations. They include endocrine and hematological disorders, kidney and joints involvement, as well as autoimmune syndromes. Cutaneous manifestations constitute a significant part of extrahepatic abnormalities. There are at least two possible explanations for pathogenesis of these disorders. Viral infection is thought to trigger autoimmune processes. which may lead to several dermatological mani-festations, particularly in individuals with some genetic predisposition. On the other hand in some cutaneous disorders replication of HCV was found in skin lesion, and direct tissue invasion by the virus should be considered. In this paper we present highly prevalent skin diseases associated with HCV infection that may become the common problem for both dermatologists and infectiologists.

Choroby skóry u pacjentów zakażonych HCV – zależności etiopatogenetyczne?

Zakażenia wirusem zapalenia wątroby typu C (HCV) stanowią jeden z ważniejszych problemów epidemiologicznych współczesnego świata. Ocenia się, że dotyczy on ponad 170 milionów osób, czyli około 3% populacji ogólnej. Powszechnie znane są konsekwencje hepatologiczne długotrwałej infekcji HCV. Jednakże coraz częściej zwraca się uwagę na liczne manifestacje pozawątrobowe, spośród których znaczną część stanowią zmiany skórne. W pracy omówiono choroby dermatologiczne towarzyszące przewlekłemu zapaleniu wątroby typu C, ze zwróceniem szczególnej uwagi na możliwe zależności etiopatogenetyczne. Nowoczesne techniki biologii molekularnej pozwalają w sposób obiektywny wykazać udział infekcji HCV w powstawaniu niektórych chorób skóry, chociaż w wielu przypadkach nie udało się dotychczas poznać szczegółowych mechanizmów patogenetycznych.