

Chair and Department of Dermatology, Chair and Department of Infectious Diseases
Medical University of Lublin

ALDONA PIETRZAK, KRZYSZTOF TOMASIEWICZ,
ROMA MODRZEWSKA, GRAŻYNA CHODOROWSKA, JANUSZ URBAN,
DOROTA KRASOWSKA

*Erythema annulare centrifugum associated with hepatitis C virus
(HCV) infection*

Viruses are known to be etiologic agents of many skin diseases. Besides, viral infection is thought to trigger autoimmune processes, which may lead to several dermatological disorders, particularly in individuals with some genetic predisposition. One of highly prevalent viral infections in humans is infection with hepatitis C virus (HCV) that also may be associated with some cutaneous manifestation.

At present, HCV infection is a major public health problem all over the world. It is responsible for at least 70% of chronic hepatitis cases. A global prevalence of HCV infection is estimated as 3% of general population (170 million individuals), who are at risk for liver cirrhosis and hepatocellular carcinoma (the annual incidence 1–4%). The future prognoses are even more dramatic, suggesting the cases of cirrhosis will increase markedly (6).

Chronic HCV infection is associated with a wide spectrum of extrahepatic manifestations, many of which may affect skin and are a common problem for dermatologists and infectiologists. Most of cutaneous manifestations are thought to be immune mediated as the consequence of monoclonal and polyclonal lymphocyte reaction (6, 7, 11).

Dermatological disorders found in HCV infected patients may be divided into three groups (11). 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 annulare* and disseminated superficial actinic porokeratosis (11).

In every case of skin disease and HCV infection coexistence the possible etiopathogenetic links were considered. The relationship is usually difficult to be proven. Mixed cryoglobulinemia (MC) is one of dermatological disorders unquestionably related to HCV infection (12). The application of sensitive PCR techniques in the detection of HCV-RNA in serum and cryoprecipitate has enabled to confirm such association. HCV-RNA sequences have been found in much higher (100–1,000-fold) concentration in the cryoprecipitate compared to serum (6). Resolution of the skin manifestations of MC after interferon treatment and relapses in case of unsuccessful chronic hepatitis C are thought to be clinical evidence (11).

Porphyria cutanea tarda (PCT) is mentioned in many handbooks as a classic skin manifestation of HCV infection. However, HCV viremia prevalence in PCT patients ranged from 62% to 100%, in several studies (16). On the other hand, Navas et al. has identified HCV-RNA in liver tissue and peripheral blood mononuclear cells of all patients with PCT, whereas it was found in serum in only 45% of cases (13). Moreover, Chiaverini et al. have proven a statistically significant increase in the C282Y mutation of hemochromatosis gene that should be considered as an additional PCT-triggering factor (2).

Even more questions have arisen around the role of HCV in the development of lichen planus (LP). In several studies from 10% to 23% of patients with LP were positive for anti-HCV (1,10,11). Recently, Kurokawa et al. have shown the presence of anti-genomic as well as genomic-strand HCV-RNAs in lichen planus lesions in patients with chronic hepatitis C. It may suggest that HCV-associated LP lesions are sites of virus replication (10). The role of HCV in other, mentioned above, skin disorders remains unclear and further studies are necessary to confirm or deny any etiopathogenetic links.

In this study we present a case report of the patient with chronic hepatitis C, in whom *erythema annulare centrifugum* developed. Because, to the best of our knowledge, so far coexistence of *erythema annulare centrifugum* and HCV infection has not been reported, we consider this case interesting.

CASE REPORT

A 29-year-old woman with a 5-year history of pruritic lesions was sent to the Department of Dermatology, Medical University of Lublin. Since 1999 the patient has presented with periodical (every 6 months) labial herpes and multiple widespread edematous and plain papules. They were 3–5 mm in diameter and the colour was dark pink. The history revealed that similar lesions were already present in adolescence period, located mostly on the dorsal side of the hand. In her opinion, there was a relationship between exposure to paint, herbal solutions and some sorts of clothes material, and skin symptoms. Six months before current admission to the clinic, the patient noticed for the first time several erosions of the oral mucosa, particularly on the palate.

On the day of clinic admission widespread pink papules were seen. They were up to 2 cm in size, erythematous and edematous, located primarily on the skin over intermetacarpal, elbow and ankle joints. Lesions size ranged from 5 mm to 25 mm and they were bordered from normal skin (Fig. 1). Additional erosions of nasal mucous membrane and grayish patch of the tongue were identified. Because bullous disorder was suspected, we started diagnostic procedures, which did not confirm the presence of acantholytic cells. The course of disease and lesions were atypical, so diagnostic examinations including markers of viral infection were carried out. The skin biopsy was also performed using local antithesis with ethyl chloride.

The patient came for a control visit 7 days later and erythematous and an edematous spot, 6 cm long in diameter, located on the dorsal surface of the left hand was present. The therapy with acyclovir was started due to prolonged labial herpes. Systemic clemastine and escin as well as topical dimetidene and topical antibiotic were introduced.

Two weeks later the central area of maculae turned pale, however margins were markedly raised. We decided to continue the therapy with acyclovir. When the patient came for a next visit 2 weeks later, new edematous papules were found located next to the old ones. Additional treatment with local troxerutin was started. During the next month the eruption of lesions had greatly improved and finally resolved. However, few weeks later a single annular lesion appeared on the right hand. It was considered to be the suspected annular granuloma and resolved one week later. On the next visit the patient had no systemic or skin symptoms. Unfortunately, 2 weeks later the new similar widespread skin lesions appeared. All of them were pruritic. They resolved 10 days later. The last observation was done 4 months after first admission. The patient came with labial herpes on the lower lip.



Fig. 1. Skin lesions of *erythema annulare centrifugum* located on hands

LABORATORY TESTS

Due to unspecific course of disease and atypical appearance of skin lesion, the exact and final diagnosis was difficult. We performed a wide spectrum of laboratory tests, including routine tests, microbiological examination and histopathology of skin biopsy.

Laboratory tests showed normal results of morphology and biochemical parameters. An abdomen ultrasonography done at the time of admission revealed no pathology. Diagnostic procedures involved serological markers of common viruses. We excluded both Epstein-Barr virus (EBV) and cytomegalovirus (CMV) primary infection. Anti-Herpes ~ IgM were negative, whereas IgG class antibodies were present. Hepatitis B surface antigen (HBsAg) and anti-HIV assays were negative, whereas anti-HCV screening test was reactive. It was detected with ImmunoComb II HCV test (indirect solid-phase enzyme immunoassay-EIA, Organics, Israel) and confirmed by a third-generation enzyme immunoassay (UBI HCV EIA4.0, Organon Teknika, Holland).

There were no laboratory positive findings concerning bacterial and fungal infection, except slightly elevated (295 IU mL^{-1} ; whereas 200 IU mL^{-1} is considered normal upper limit) anti-streptolysine O assay (ASO). The tests for autoantibodies were also negative. Antinuclear (ANA) and antimitochondrial antibodies (AMA) were absent. Immunofluorescence tests for the presence of anti-pemphigus and anti-pemphigoid were negative. Waalery-Rose test was negative and CRP2 level remained in normal ranges.

Morphology and biochemical tests of blood, except liver aminotransferase levels, demonstrated no abnormal values. White blood cells count was $5.2 \text{ K } \mu\text{L}^{-1}$ and consisted of bands – 2%, granulocytes – 52%, eosinophils – 2%, lymphocytes – 41% and monocytes – 3%. Total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, total protein and albumin level were normal. Alanine aminotransferase (ALT) was 49 IU (normal, $<31 \text{ IU}$) and aspartate aminotransferase (AST) was 39 IU (normal, $<31 \text{ IU}$).

Capillaroscopy was done in June 2004 and has showed the presence of dermal capillaries loops with short and narrow branches, and lack of Raynaud loops. Light test with UVA was negative, whereas with UVB was positive after 2.5 minutes.

We had expected the histopathology of skin lesions would be helpful and it was. The specimen included epidermis and dermis. It showed a dense perivascular lymphohistiocytic infiltrates of the superficial layers of dermis. Besides, additional minimal spongiosis was found and edema of papillary dermis (Fig. 2). The diagnosis of *erythema annulare centrifugum* was made.

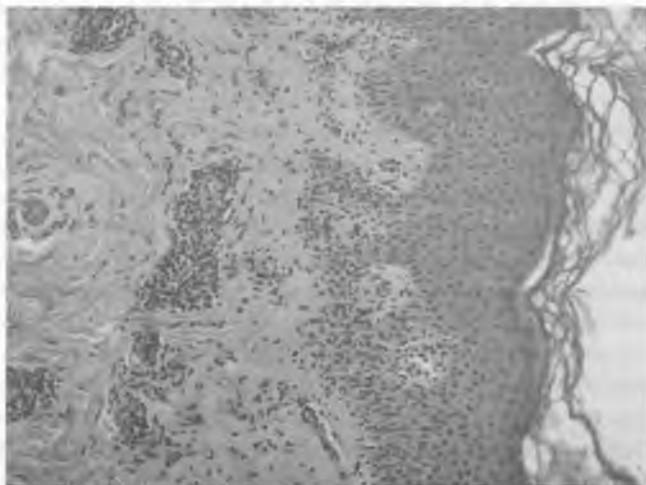


Fig. 2. Histopathology of skin lesions showing dense perivascular lymphohistiocytic infiltrates of the superficial layers of dermis. Besides, additional minimal spongiosis and edema of papillary dermis are seen

Due to anti-HCV finding, the patient was admitted to the outpatients' clinic at the Department of Infectious Diseases in July 2004. We have confirmed the presence of HCV-RNA, and the viremia level was 7.28×10^4 copies/mL, using RT PCR HCV Test v.2.0Amplicor Monitor, Roche. The genotype 1b of HCV was found in test HCV Genotype Assay (LiPA), Bayer. We have planned to perform liver biopsy, but finally the patient informed us she was in 4th week of gestation. Further diagnostic procedures (liver biopsy) and possible treatment with PEG-Interferon and Ribavirin have been postponed.

DISCUSSION

The case we report here has been characterized with no typical symptoms and appearance of skin lesions. The diagnosis was really difficult and several various concepts, such as pemphigus, *erythema multiforme exudatum* and Sweet syndrome were considered. The final diagnosis was made based on the histopathology of skin biopsy.

Erythema annulare centrifugum (EAC) has been categorized into superficial and deep variants (8, 18). The case we report here represents the superficial type. The pathogenesis of both types of EAC is not fully explained. It is thought to represent a cutaneous hypersensitivity to diverse causes, including infectious agents, drugs, malignant neoplasms and even ingestions (4, 5, 9, 15, 17). Unfortunately, these possible ethiopathogenetic links are documented for relatively small number of patients, and interpretation should be very careful.

To the best of our knowledge there is only one report of EAC case with underlying liver disease (except cases of bile duct obstruction (15). In 2004 Gulati et al. have reported the case of a child with autoimmune hepatitis and EAC. Although this patient was also positive to anti-HCV, HCV-RNA was negative. Due to various serological abnormalities in the course of autoimmune hepatitis (5), anti-HCV were considered as possibly false positive. The infection of HCV in our patient has been confirmed with PCR method and genotype 1b was found. The liver biopsy has not been performed, because the patient got pregnant. The mechanisms of possible pathogenetic link between these two disorders is difficult to establish, however due to the fact that HCV infection is associated with various extrahepatic manifestations it should be treated as possibly causally related to HCV infection.

Another etiologic infectious agent that should be taken into consideration is *Herpes simplex*. Recurrent labial herpes has been diagnosed in the patient many times in the past.

Because the patient is currently pregnant, she needs to be observed carefully by different specialists. We are eager to know, how the pregnancy may influence the skin lesions of EAC. We have found two reports concerning the presence of EAC in pregnancy (3, 14). Choonhakaran and Seramethakun have observed the rapid improvement of skin lesions after delivery (3).

We believe our case report may help to pay attention to possible HCV infection in patients with EAC. Although anti-HCV test is not a routine one, we would suggest screening of all the patients with EAC.

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SUMMARY

Chronic HCV infection is associated with a wide spectrum of extrahepatic manifestations, many of which may affect skin and are a common problem for dermatologists and infectiologists. Most of cutaneous manifestations are thought to be immune mediated as the consequence of monoclonal and polyclonal lymphocyte reaction. A first case report of the patient with chronic hepatitis C, in whom *erythema annulare centrifugum* (EAC) developed is discussed. A 29-year-old woman with pink papules was seen. The papules were up to 2 cm in size, erythematous and edematous, located primarily on the skin over intermetacarpal, elbow and ankle joints. Lesions size ranged from 5 mm to 25 mm and they were bordered from normal skin. The diagnosis of *erythema annulare centrifugum* was made based on histopathology of the skin. An active HCV genotype 2b infection was the only additional finding. The possible etiopathogenic link between EAC and HCV infection was discussed. As the virus has a great influence on the immunologic system, it should be considered as a possible triggering factor for EAC. We would suggest HCV screening of all the patients with EAC.

Erythema annulare centrifugum w przebiegu zakażenia HCV

W przebiegu zakażenia HCV obserwuje się objawy pozawątrobowe, które mogą obejmować zajęcie skóry i stanowić wspólny problem dla dermatologów i lekarzy chorób zakaźnych. W większości przypadków uważa się, że mogą stanowić konsekwencje monoklonalnej i poliklonalnej odpowiedzi limfocytów na zakażenie. Po raz pierwszy przedstawiamy przypadek pacjentki z przewlekłym zapaleniem wątroby typu C, u której doszło do rozwoju zmian skórnych rozpoznanych jako *erythema annulare centrifugum* (EAC). 29-letnia pacjentka zgłosiła się do przychodni dermatologicznej z powodu pojawienia się różowych grudek. Zmiany o średnicy do 2 cm, dobrze odgraniczone od zdrowej skóry, były zlokalizowane przede wszystkim na skórze dłoni, łokci i w okolicy stawów skokowych. Rozpoznanie *erythema annulare centrifugum* postawiono na podstawie badania histopatologicznego. W związku z podwyższoną aktywnością aminotransferaz przeprowadzono diagnostykę hepatologiczną i stwierdzono aktywne zakażenie HCV genotypem 2b. Nie wykonano biopsji wątroby, ponieważ pacjentka zaszła w ciążę. Omówiono możliwy związek etiopatogenetyczny pomiędzy EAC i zakażeniem HCV. W związku z istotnym wpływem infekcji HCV na układ immunologiczny należy brać pod uwagę rolę wirusa jak czynnika wyzwalającego rozwój EAC. Zasadne wydaje się wykonywanie badań skriningowych w kierunku zakażenia HCV u wszystkich pacjentów z EAC.