Chronic Hepatitis C Virus Infection Associated with Dermatomyositis and Hepatocellular Carcinoma

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Dermatomyositis is a rare and idiopathic inflammatory myopathy with characteristic cutaneous manifestations. In recent years, some researchers have showed the cause of dermatomyositis might be due to an autoimmune response induced by viral infections. However, chronic hepatitis C virus (HCV) infection associated with dermatomyositis is very rare. In this report, we present a patient with dematomyositis with abnormal liver function test results and elevated alfa-fetoprotein level. After excluding multiple viral infections known to cause myositis, the case was proven to be chronic hepatitis C by positive HCV-RNA in the serum. Abdominal computed tomography showed a liver tumor on the right lobe and needle biopsy proved it to be hepatocellular carcinoma. Chronic hepatitis C or hepatocellular carcinoma might cause dermatomyositis by inducing the formation of autoantibodies. Chronic hepatitis C or hepatocellular carcinoma should be considered in patients of dermatomyositis if no other cause is found. *(Chang Gung Med J 2004;27:834-9)*

Key words: hepatitis C virus, dermatomyositis, hepatocellular carcinoma.

Hepatitis C virus (HCV) infection is a common cause of liver disease. Long-term chronic HCV infection may lead to liver cirrhosis and hepatocellular carcinoma (HCC). In recent years, some researchers have showed that HCV might be associated with autoimmune manifestations,[1] such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis, membranoproliferative glomerulonephritis, Sjogren's syndrome, and mixed cryoglobulinemia with the formation of autoantibodies and circulating immune complexes. Chronic HCV infection might cause autoimmune manifestations by inducing the formation of autoantibodies. However, HCV infection associated with dermatomyositis is very rare. We present a patient with chronic HCV infection associated with HCC and dermatomyositis.

CASE REPORT

A 71-year-old man had been healthy , however, he began to suffered from progressive weakness in his bilateral hips and thighs, difficulty in combing his hair, dysphagia, and erythematous changes of the skin over his face, upper chest and neck for about 3 weeks. There was history of no blood transfusion, tattooing, or intravenous drug addiction in this patient. Physical examination revealed heliotrope rash with bilateral periorbital edema, violaceous papules over the scalp, and poikiloderma on the upper chest and neck. Musculoskeletal examination showed marked weakness of all proximal muscles of the extremities symmetrically.

Laboratory data showed levels of serum creatine

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kinase (CK): 674 IU/L (15-130), lactate dehydrogenase (LDH): 215 IU/L (47-140), aspartate aminotransferase (AST): 128 IU/L (0-34), alanine aminotransferase (ALT): 68 IU/L (0-36), albumin: 2.4 g/dl (3.5-5.5), and total bilirubin: 1.3 mg/dl (0-1.3). Antinuclear antibody was positive (1:80, speckled). Other autoantibodies, including anti-ENA, anti double-strand DNA, anti-RNP, anti-Sm, anti-SSA, anti-SSB, anti-Scl 70 and anti-Jo-1, were all negative. The results of the complete blood count were normal. Electromyography showed a small amount of polyphasic waves with normal interference pattern in all muscles tested. Skin biopsy of the right upper arm showed a sparse lymphocytic infiltration around the blood vessels and negative results on the immunofluorescent study (Fig. 1), which is compatible with dermatomyositis.

Tumor markers were checked under suggestion of underlying malignant disease. CEA, CA199 and PSA were normal but he had marked elevation of alpha-fetoprotein of up to 21051 ng/ml. Abdominal sonography and computer tomography revealed a 6.5-cm liver tumor on the right lobe (Fig. 2) and liver cirrhosis. Liver tumor needle biopsy pathology showed hepatocellular carcinoma. Hepatitis B virus surface antigen was negative, and antibody to HCV was positive using enzyme linked immunoabsorbent assay. HCV infection was confirmed by the presence of HCV-RNA in the serum with reverse transcriptase polymerase chain reaction amplification. Serum antibody titers of human immunodeficiency virus (HIV), coxsackieviruses, adenovirus, influenza virus, human T leukemia/lymphoma virus type I (HTLV-1) and rubella virus were not elevated.

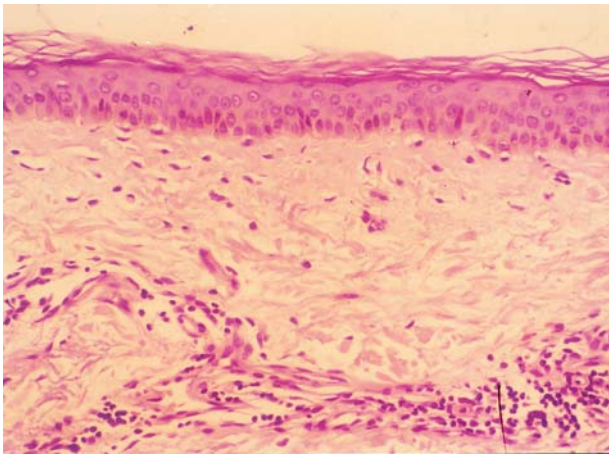

Fig. 1 Skin biopsy of right upper arm with haematoxylin + eosin stain (×66 objective) shows flattened epidermis and a scattered inflammatory infiltrate around the capillaries of the dermis.

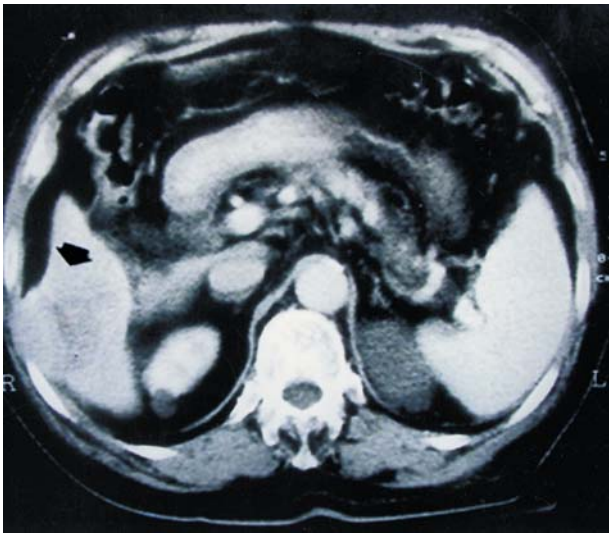

Fig. 2 Abdominal computed tomography shows a 6.5-cm tumor at the right lobe of the liver (arrow).

A total of 30 mg of oral prednisolone was given per day and his muscle power improved slightly. Prednisolone was stopped 2 weeks after beginning the administration due to active bleeding of gastroduodenal ulcers. Transcatheter arterial embolization and local injection therapy for liver tumor were not performed because of poor liver function.

DISCUSSION

The criteria to define dermatomyositis were first proposed by Bohan and Peter in 1975.[2] Patients with dermatomyositis who have typical skin rash, symmetrical proximal muscle weakness, electromyography findings, and elevation of serum creatine kinase may not require a muscle biopsy to confirm the diagnosis.

The etiology and pathogenesis of dermatomyositis are still unknown, but it is believed to be a disorder of the autoimmunity that is triggered by environmental factors in genetically susceptible indi-

viduals. The increased frequency of HLA-DR3 and HLA-DRw52 antigens in these patients suggests an underlying genetic predisposition.[3]

The results of tests for multiple viral infections, such as coxsackieviruses, HIV, HTLV-1, echovirus, influenza, adenovirus and hepatitis B, which are known to cause myositis, were all negative in this patient. Antibodies that attack a virus or virus-enzyme complex could cross react with homologous area of host proteins and result in autoantibody production, which is called a cross-reactive phenomenon. Anti-aminoacyl-tRNA synthetases are the most commonly recognized myositis-specific autoantibodies, such as anti-Jo1 and anti-Mi2 autoantibodies. Circulating immune complexes or autoantibodies might induce dermatomyositis of this patient. HCV may interact with aminoacyl-tRNA synthetase, which is the target of several myositis specific autoantibodies.[4]

Only 11 cases of dermatomyositis and HCV infection have been reported in the literature (Table 1).[5-11] Some cases also had other autoimmune diseases, such as autoimmune thrombocytopenic purpura, cryoglobulinemia, collagenous colitis, acquired ichthyosis and interstitial pneumonitis. HCV was found during an endomyocardial biopsy in a patient of dermatomyositis associated with left ventricular dysfunction.[9] In thecases reported in the literature, three cases had been infected with HCV before dermatomyositis was diagnosed and the other eight cases of dermatomyositis had been diagnosed with HCV infection incidentally. We speculated that these cases might also have had long-term chronic HCV infection and induced dermatomyositis by the autoantibodies. The use of immunosuppressive agents, such as steroid and azathioprine, may improve the symptoms of myositis clinically in some cases,[5,7,8,11] however, hepatitis C viremia was noted to be persistent in these cases after the treatment. Long-term effects and complications of immunosuppressive agents need further investigations.

An association between malignancy and dermatomyositis has been widely reported in the literature, with an incidence ranging from 7 to 30%.[12] These malignancies include ovarian cancer, breast cancer, cervical cancer, esophageal cancer, sigmoid

Table 1. Comparisons of 11 Cases of Dermatomyositis (Derm) Associated with Chronic Hepatitis C Virus (HCV) Infection

Case (Ref)	Years	Age (years)	Gender	Diagnosis of HCV and Derm	Anti-Jo-1 antibody	Associated disorders	Antinuclear antibody
1[5]	1994	48	Male	Coincident	Not done	Nil	Negative
2[6]	1996	72	Male	Coincident	Positive	Nil	Negative
3[6]	1996	70	Male	Coincident	Positive	AIDS	Negative
4[6]	1996	65	Male	Coincident	Positive	Interstitial pneumonitis; Raynaud phenomenon	Negative
5[6]	1996	-	Female	Coincident	Positive	Liver cirrhosis, Hepatitis B, Cryoglobulinemia	Negative
6[6]	1996	68	Male	Coincident	Positive	Hepatitis B	Negative
7[7]	1997	73	Male	Coincident	Positive	HCC	Positive
8[8]	1998	65	Female	4 years earlier of HCV	Positive	Autoimmune thrombocytopenic purpura	Positive
9[9]	2000	60	Female	6 years earlier of HCV	Negative	Left ventricular dysfunction Myocardial biopsy: HCV positive	Negative
10[10]	2001	51	Male	7 years earlier of HCV	Negative	HCC, Acquired ichthyosis	Positive
11[11]	2002	40	Female	Coincident	Negative	Collagenous colitis	Negative
Our case	2003	71	Male	Coincident	Negative	HCC, Liver cirrhosis	Positive

Table 2. Comparison of 6 Cases of Dermatomyositis Associated with Liver Cancer

Case (Ref)	Year	Anti-HCV	Age (years)	Gender	Histopathology
1[15]	1976	Not done	36	Male	HCC
2[16]	1989	Not done	56	Female	Combined HCC-CCC
3[7]	1997	Positive	73	Male	HCC
4[10]	2001	Positive	51	Male	HCC
Our case	2003	Positive	71	Male	HCC

Abbreviations: HCC: hepatocellular carcinoma; HCC-CCC: hepatocellular carcinoma-cholangiocellular carcinoma.

cancer, lung cancer, and nasopharyngeal carcinoma. Anti-Mi2 autoantibodies were found in a few cases of dermatomyositis (20%) and cancer-associated myositis.[13] In an animal study, a 169bp cDNA product, which was isolated from H4IIE rat hepatoma cells, was 88% homologous to the human Mi2 autoantigen. At the protein level, there was 100% homology. Anti-Mi2 autoantibodies may be cross reactive with rat hepatoma cells and cause dermatomyositis.[14]

In the review of the literature, only four cases had both dermatomyositis and HCC (Table 2).[7,10,15,16] Since HCV was identified in 1989,[17] HCV screening tests were not performed in the case reports[15,16] published before 1989. Long-term chronic HCV infection is a major risk factor for the development of HCC. Dermatomyositis of these cases might also have a strong association with HCV infection.[18] There is no direct evidence showing dermatomyositis of these cases was induced by HCC through the cross-reactive phenomenon, however, the relationship between dermatomyositis and HCC needs further investigations.

In summary, dermatomyositis of our patient might have been caused by chronic HCV infection through the autoimmune mechanism. Chronic HCV infection or HCC should be considered as a cause of dermatomyositis, if there is no other etiology found.

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慢性C型肝炎病毒感染合併皮肌炎及肝癌

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皮肌炎是一種不明原因的發炎性肌肉病變合併典型的表皮特徵。近年來，有些報告顯示造成皮肌炎的原因可能與病毒感染後誘發自體免疫反應有關，但慢性C型肝炎病毒感染合併皮肌炎卻非常罕見。本篇報告一位被診斷爲皮肌炎病人合併有肝指數異常及胎兒蛋白上升，經排除其他已知引起皮肌炎的病毒感染後，病人血清C型肝炎病毒檢查爲陽性，證實爲慢性C型肝炎。腹部電腦斷層發現肝腫瘤，肝切片證實爲肝癌。慢性C型肝炎或肝癌可能經由誘發自體抗體的產生而造成皮肌炎，在皮肌炎的病人若找不到其他原因時，應考慮是否有慢性C型肝炎感染或是肝癌。(長庚醫誌2004;27:834-9)

關鍵字：C型肝炎，皮肌炎，肝癌。

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