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The coexistence of sarcoidosis and hepatitis C: A case report

Hepatit C ve sarkoidozis birlikteliği: Olgu sunumu

Ahmet ERDİL[1], Ahmet TÜZÜN[1], Abdurrahman KADAYIFÇI[2], Ahmet UYGUN[1], İsmail YÜKSEKOL[3], M. Salih DEVECİ[4], Kemal DAĞALP[1]

Gulhane Military Medical Academy, Department of Gastroenterology[1], Chest Disease[3] and Pathology[4] Ankara
Gaziantep University Department of Gastroenterology[2], Gaziantep

Sarcoidosis is a multisystemic, chronic granulomatous disorder of unknown etiology. Although a number of infectious and non-infectious causes have been suggested, no specific agent has been identified as yet. Hepatitis C virus infection may result in chronic hepatitis and cirrhosis and extrahepatic manifestations of Hepatitis C virus include autoimmune and rheumatic diseases and a high prevalence of autoantibodies. The association of sarcoidosis with hepatitis C infection has been reported rarely. We report the case of an asymptomatic chronic Hepatitis C virus infection found in a young male patient following prednisolone treatment for pulmonary sarcoidosis. The coexistence of both diseases in the same patient suggested that chronic hepatitis C infection might play a part in the occurrence of sarcoidosis via an undetermined immunopathogenic mechanism.

Key words: Sarcoidosis, chronic HCV infection.

Sarkoidozis etyolojisi bilinmeyen, multisistemik kronik granülamatöz bir hastalıktır. Etyolojide bir çok enfeksiyöz ve non-enfeksiyöz nedenler düşünülmüşse de, henüz spesifik bir ajan bu durumdan sorumlu tutulamamıştır. Hepatit C virüs enfeksiyonu kronik hepatit ve siroza neden olabilen bir hastalıktır. Hepatit C virüs enfeksiyonunun ekstrahepatik bulguları içinde otoimmün ve romatizmal hastalıklar sık görülmekte olup, yapılan bir çok çalışmada Hepatit C virüs enfeksiyonunda otoantikor yapımında artma tespit edilmiştir. Bir erkek hastada pulmoner sarkoidozis nedeniyle prednizolon tedavisinden sonra asemptomatik kronik Hepatit C virüs enfeksiyonu tespit edildi. Aynı hastada her iki hastalığın birlikte bulunması, kronik hepatit C enfeksiyonunun bilinmeyen immünopatojenik bir mekanizmayla sarkoidosiz oluşumunda rol oynayabileceğini düşündürmektedir.

Anahtar kelimeler: Sarkoidozis, kronik HCV enfeksiyonu.

INTRODUCTION

Sarcoidosis is a multisystemic, chronic granulomatous disorder of unknown etiology. Although a number of infectious and non-infectious causes have been suggested, no specific causative agent has yet been found responsible for the disease. However, an exaggerated cellular immune response to a certain class of antigens or self-antigens is generally accepted to be a factor in the etiopathogenesis of the disease (1). There is also some evidence consistent with the theory of autoimmunity in sarcoidosis. Hepatitis C virus (HCV) infection may result in chronic hepatitis and cirrhosis and extrahepatic manifestations of HCV, including autoimmune and rheumatic diseases and a high prevalence of autoantibodies have been shown in many studies (2). In recent years sarcoidosis associated with interferon-alpha (IFN) therapy for chronic hepatitis C has been reported as a rare side effect of IFN treatment (3-5). However, the coexistence of pulmonary sarcoidosis and chronic HCV infection in the absence of IFN treatment has not been reported. In this paper, we describe a young patient in whom both sarcoidosis and chronic HCV infection occurred, with the HCV infection having been activated by prednisolone treatment.

CASE

A 22 year-old male patient was referred to our hospital with fatigue, malaise, anorexia, weight loss, dyspnea and polyarthralgia. Bilateral hilar adenopathy with minimal parenchymal reticulonodular infiltration was detected in the routine

Address for correspondence: Dr. Ahmet ERDİL
GATA Lojmanlari, Ural apt. No:9, Etlik Ankara
Phone: 90 312 3262334 Mobile: 90 542 6107912
Fax: 90 312 3217778
E-mail: ahmeterdil@yahoo.com

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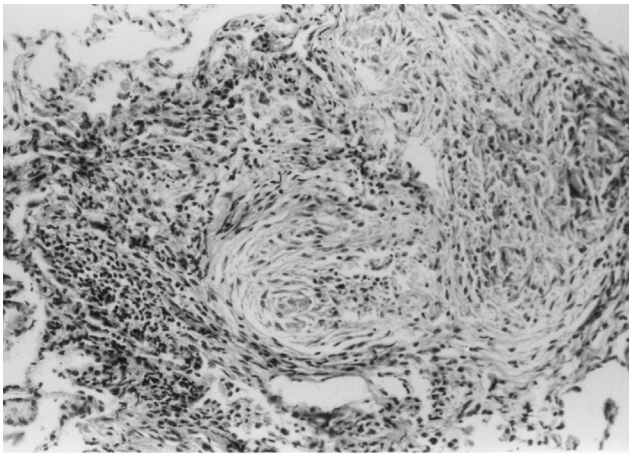

Figure 1. Characteristic sarcoid noncaseating granulomas in lung (Hematoxylin-Eosin, X100).

chest film, with computed tomography of the chest confirming these findings. Bronchoalveolar lavage demonstrated a significant increase in the proportion of T-lymphocytes with an elevated ratio of CD4/CD8. Transbronchial biopsy of lung parenchyma revealed several typical sarcoid-like noncaseating granulomas composed of Langhans-type giant cells and epitheloid histiocytes (Figure 1). As no acid-fast organism was observed by Ziehl-Neelsen method, grade II pulmonary sarcoidosis was diagnosed. Laboratory findings were as follows: serum calcium: normal, angiotensin-converting enzyme: slightly elevated, antinuclear antibodies: negative, serum globulin level: increased and anti-HIV negative. Pulmonary function tests revealed a moderate decrease in lung volumes with a normal ratio of forced expiratory volume in one-second to the forced vital capacity. No involvement of other organs could be detected in routine examinations and laboratory tests. The patient was given prednisolone 1 mg/kg and the dose was gradually tapered after the fourth week. The patient improved and the chest film improved significantly by the second month. At follow-up however, a significant elevation in serum hepatic enzyme levels was detected, with an alanine aminotransferase (ALT) level of 219 U (normal range 0-40) and aspartate aminotransferase (AST) level of 91 U (normal range 0-40). On investigation of the cause of this elevation, serum anti-HCV and HCV-RNA were found to be positive while other hepatitis markers (including anti-HAV IgM, HBsAg, anti-HBs anti-HBc IgM and HGV-RNA) and autoantibodies (including antinuclear antibody, anti-DNA, anti-microsomal antibody and anti-smooth muscle antibody) were negative. Histopathologic examination of liver revealed moderate portal inflammation with piecemeal necrosis, minimal necroinflammation and fibrosis. These findings were consistent with chronic moderately active HCV infection. The patient had a history of blood transfusion five years previously. The steroid treatment was stopped and serum ALT and AST levels returned to normal range within three months. Serum HCV-RNA disappeared following the steroid treatment. The patient was followed up without any treatment and had no significant symptom related to sarcoidosis and liver disease at six-month follow-up although anti-HCV was still positive.

DISCUSSION

Various extrahepatic diseases and findings have been reported in association with HCV infection. Among these, mixed cryoglobulinemia, leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, thyroiditis, Sjögren syndrome, lichen planus, porphyria cutanea tarda and high prevalence of autoantibodies are known to be associated with chronic infection (2). In most cases the pathogenesis of these conditions in HCV infection is not precisely known in most cases. However, there is convincing evidence that immune-mediated mechanisms including immune complexes deposition, specific T lymphocytes activation or autoantibodies formation, effects of cytokines and mono or polyclonal induction of lymphocytes are factors in the pathogenesis of HCV-related extrahepatic manifestations (6).

HCV infection induces a virus-specific immune response in the body in addition to a non-specific immune activation. Virus-specific immune response includes both humoral and cellular components. CD4+ T-cell response to HCV proteins is the main cellular immune activation for host protection in infected individuals. It enhances antibody production from B cells and activates suppressor T lymphocytes. Therefore, CD4+ T-cell response to HCV has been assessed as a protective reaction. CD4+ T cells transform mainly to T-helper 1 and a lesser extent to T-helper 2 cells after resolution of the acute phase for the control of viral replication (7).

Although the etiology of sarcoidosis is unknown,

numerous evidence indicates that it results from a cellular immune activation response to various antigenic stimuli. An increased helper T-cell response is the main cause of this activation. It has been shown that an intensive accumulation of T-helper lymphocytes occurs in the affected organs of sarcoidosis. Activated helper T-cells release a number of mediators activating phagocytes and possibly causing granulomatous reaction (1).

As yet, it is not possible to confirm the coexistence of HCV infection and sarcoidosis. In fact, Mert et al. Found no increase in HCV prevalence in patients with sarcoidosis (8). This coexistence may therefore be a coincidence but should be taken into consideration since similar immune pathogenic mechanisms are involved in the course of both diseases. It is possible that activated T-helper response in HCV infection along with some other host factors might induce the release of certain mediators and activation of mononuclear phagocytes, that finally causes a sarcoid-like granulomatous reaction. Glucocorticoids improve the symptoms while effectively suppressing the activated T-helper cells in sarcoidosis, but activate chronic hepatitis since T-helper cells mainly control viral replication in HCV infection. The manifestation of underlying chronic HCV infection after glucocorticoid treatment in our patient confirms this concept and shows the importance of T-helper cells in the pathogenesis of both diseases. On the other hand, our patient underwent some invasive diagnostic procedures, such as bronchoscopy, which could be a potential cause of HCV acquisition. However, histopathological examination of liver biopsy revealed definitive findings of chronic HCV infection.

Sarcoidosis associated with interferon-a therapy has been described in several case reports in recent years (3-5). Interestingly, most of the patients in these reports had received interferon therapy for hepatitis C infection, although this drug has also been used widely in numerous diseases such as hepatitis B, chronic myelogenous leukemia, idiopathic trombocytopenic purpura, renal cell carcinoma and dermatological diseases. When all the literature reports were evaluated, sarcoidosis occurred during or after the end of interferon treatment in five cases of hepatitis C but recurred in only one patient with a known history of sarcoidosis in remission. The immunomodulator effect of interferon on T-helper cells was suggested to be a triggering mechanism for the development of sarcoidosis in these patients. However, the link between Interferon related sarcoidosis and hepatitis C is obscure in these reports. It is the view of the present authors that some patients with hepatitis C may have a tendency to sarcoidosis due to underlying immune abnormalities. An undetectable triggering mechanism or interferon may induce the development of sarcoidosis in only a small number of these patients.

The coexistence of sarcoidosis and hepatitis C in an individual patient associated with or without interferon treatment could arise from a similar immunopathogenic mechanism. This phenomenon requires further investigation that may allow a better understanding of the pathogenesis of sarcoidosis. Thus it was considered that this case report contributes to an improved understanding in that it is the first such report emphasising the coexistence of pulmonary sarcoidosis and hepatitis C in the absence of IFN treatment.

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