ANNALS OF HEPATOLOGY

Volume 1 *Number* 2 *April-June* 2002

Article:

Epithelioid granulomas in a patient with hepatitis C virus

Annals of hepatology 2002; 1(2): April-June: 91-93

Annals of hepatology

Case Report

Epithelioid granulomas in a patient with hepatitis C virus

Raúl Pichardo-Bahena[1] and Nahum Méndez-Sánchez[2]

Abstract

Hepatitis C virus infection causes an epidemic disease. The morphologic aspects of hepatitis C infection (HCV) are well established with regards to necroinflammatory processes and consequences like fibrosis, cirrhosis, and related neoplasms. However, the presence of epithelioid granulomas has not been well described for this infection. We report a patient with HCV and granulomas without any other co-infection or history of drug abuse.

Key words: Hepatitis C, granulomas tuberculosis.

Introduction

Cases of granulomatous hepatitis are well characterized in terms of their infective and idiopathic etiology and association with drugs and HIV co-infection.[1-3] Etiologically, granulomas may be infective or non-infective. The infective causes include bacteria, fungi, mycobacteria, and viruses *(Table I).* In the non-infective types, the causes may be sarcoidosis, drugs or idiopathic *(Table II).* The drug causes include non-steroidal anti-inflammatory drugs, antibiotics, contrast medium, anti-convulsive agents, and drugs used for treatment of HCV infection. Thus, there is an extensive spectrum of etiologies.

Case report

A 40-year-old male Mexican was admitted to hospital for evaluation of hypertransaminasemia (alanine aminotransaminase 63 U/L; aspartate aminotransferase 40 U/L) and painful neck and shoulders. Chronic active hepatitis caused by the hepatitis C virus was diagnosed. Serum HCV RNA concentration was 1,000,000 copies/mL, and the viral genotype was 1b. Further examination was instituted because of the simultaneous finding of granulomas in a liver biopsy. The patient did not give a history of any use of intravenous drugs and we found no other co-infections by laboratory tests.

Discussion

The morphological aspects of HCV infection have been described during the past three decades.[4-8] These differing morphological and clinical diseases were first reported as non-A, non-B hepatitis.[9-11] In 1989, the viral agent, HCV, was identified and isolated,[12,13] and almost all cases of non-A non-B hepatitis were related to this viral agent. Most histopathological changes have been described following percutaneous or transjugular biopsies.

The histopathological changes are reported according to the hepatic area affected: the portal and periportal areas and the hepatic parenchyma. The disease is described in terms of the duration of chronic hepatitis, with activity in different grades,[7,14,15] steatosis and fibrosis. The spectrum of histological changes is related to the degree of lymphocyte or lymphoplasmocyte infiltration into the liver, and to the necroinflammatory damage caused. The pathological and pharmacological investigations aim to evaluate the fibrosis and arrest it.

How can we explain the prevalence of granulomas in clinical hepatitis C? This is an item not well described for these patients, because publications have not identified granulomas in liver biopsies of patients with HCV, by Tru-cut needle, trans-jugular or open biopsies. However, other investigators have reported granulomas in patients with HCV infection without any other infectious agent, such as in liver-transplant patients with viral flare-ups[16] and following HIV infection.

Only a few articles have mentioned the presence of epithelioid granulomas in the spectrum of chronic inflammation in patients with HCV.[17] Morphologically, granulomas are associated with central necrosis surrounded by a rim of lymphocytes, similar to that observed in cases of tuberculosis. This is our only experience of hepatic granulomas in a patient with HCV infection unrelated to HIV infection, drugs or drug abuse *(Figure 1).* In this patient, in the open liver biopsy the hallmark histological changes of liver were the presence of epithelioid granulomas with central necrosis encircled by lymphocytes and fibrosis. No birefringent material or bile extravasations were detected. No acid-fast organism (AFO) was demonstrated. However, the morphological changes were suggestive of tuberculosis granulomas. Emile et al.[17] described five patients in whom no AFOs were demonstrated.

[1] Department of Pathology.
[2] Biomedical Research and The Liver Unit.

Address for correspondence:
Raúl Pichardo-Bahena.
Medica Sur Clinic & Fundation Puente de Piedra Num. 150. Colonia Toriello Guerra, Tlalpan, C.P. 1505. Mexico, City, Mexico.

Both tuberculosis and HCV infections are diseases of global distribution, with high prevalence and with the characteristics of epidemics and endemic diseases. The presence of HCV infection and epithelioid granulomas in liver without any AFO demonstrated by histological techniques requires further study with polymerase chain reaction (PCR) technique to eliminate the other possible causes.

Table I. List of the etiologies of granulomas.*

Actinomycosis	Leprosy
Adenoma, liver cell	Leukemia, hairy cell
Alcoholic fatty liver	Listeriosis
Ascariasis	Lymphoma, Hodgkin's and non-Hodgkin's
Bacterial sepsis	Melioidosis
Boutonneus fever	Mucolipidosis II
Brucellosis	*Mycobacterium avium-intracellulare* infection
Candidiasis	Nocardiosis
Cat-scratch disease	Nonalcoholic steatohepatitis (secondary to jejunoileal bypass)
Chronic granulomatous disease of childhood	Nonspecific reactive hepatitis
Coccidioidomycosis	Paracoccidioidomycosis
Cryptococcosis	Penicilliosis
Cytomegalovirus infection	Polyarteritis nodosa
Drugs/toxins	Primary biliary cirrhosis
Eosinophilic gastroenteritis	Q fever
Epstein-Barr virus infection	Rheumatoid arthritis
Farber's lipogranulomatosis	Salmonellosis
Fascioliasis	Sarcoidosis
Foreing body giant cell reaction	Schistosomiasis
Hepatocellular cercinoma, fibrolamellar type	Syphilis, congenital, secondary and tertiary
Histoplasmosis	Systemic lupus erythematosus
Hydatid cyst	Toxoplasmosis
Idiopathic granulomatous hepatitis	Tuberculosis
Inflammatory pseudotumor	Visceral larva migrans
Langherhan's cell histiocytosis	Whipple's disease
Leishmaniasis	Zygomycosis

* From Kanel GC, Korula J: Granulomas, in Kanel and Korula, Liver Biopsy Evaluation. Philadelphia, Penn, Saunders 2000, p 43.

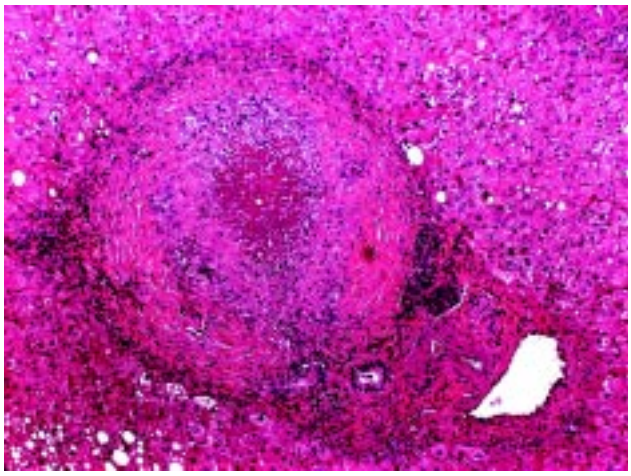

Figure 1. Hepatic granuloma, with central necrosis.

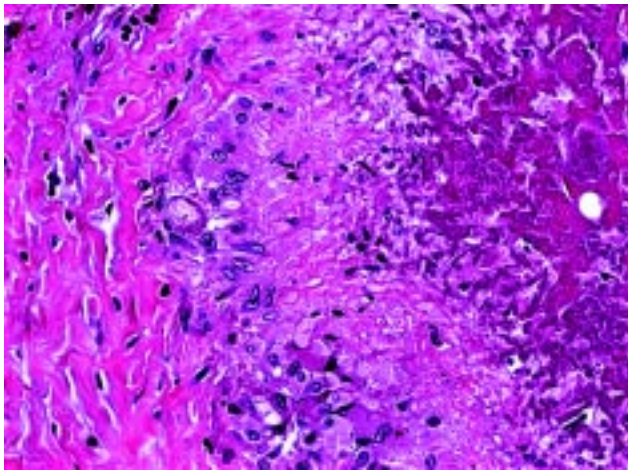

Figure 2. Central necrosis encircled by epithelioid histiocytes.

Table II. List of the drugs causing granulomas.**

Allopurinol	Dimethicone	Oxacillin	Ranitidine
Alpha-methyldopa	Disopyramida	Oxyophenbutaz-one	Silica
Aspirin	Feprazone	Oxiphenisatin	Succinylsulfathiazole
Bacille Calmette-Guérin therapy or vaccination	Glibenclamide	Papaverine	Sulfadiazine
Barium	Gold sodium thiomalate	Penicillin	Sulfadimehoxine
Beryllium	Gree-lipped mussel	Phenazone	Sulfadoxine-pyrimethamine
Carbamazepine	Halogenated hydrocarbons	Phenprocoumon	Sulfanilamide
Carbutamide	Isoniazid	Phenylbutazone	Sulfasalazine
Cephalexin	Mestranol	Polyvinyl pyrrolidone	Sulfonamides
Chlorpromazine	Metolazone	Prajmalium	Sulfonylurea agents
Chlorpropamide	Mineral oil	Procainamide	Thorotrast (thorium dioxide)
Copper	Nitrofurantoin	Procarbazine	Tocainide
Dapsone	Norethyndrone	Pronestyl	Tolbutamide
Diazepam	Norethynofrel	Quinidine	Trichlormethiazide
Diltiazem	Norgestrel	Quinine	Trimethroprim-sulfamethoxazole

** From Kanel GC, Korula J: Granulomas, in Kanel and Korula Liver Biopsy Evaluation. Philadelphia, Penn, Saunders 2000, p 221.

References

1. Ishak KG, Zimmerman HJ. Drug-induced and toxic granulomatous hepatitis. Baillieres Clin. *Gastroenterol* 1988; 2: 463-80.
2. Ryan BM, McDonald GS, Pilkington R, Kelleher D. The development of hepatic granulomas following interferon-alpha 2b therapy for chronic hepatitis C infection. *Eur J Gastroenterol Hepatol* 1998; 10: 349-51.
3. Murthy BVR, Pereira BJ. A 1990s perspective of hepatitis C, human immunodeficiency virus, and tuberculosis infections in dialysis patients. *Semin Nephrol* 1997; 17: 346-63.
4. Bach N, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis: a comparative analysis. *Hepatology* 1992; 15: 572-77.
5. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991; 13: 372-74.
6. Scheuer PJ, Ashrafzadeh P, Sherlock S, Brown D, Dusheiko GM. The pathology of hepatitis C. *Hepatology* 1992; 15: 567-71.
7. Ishak KG. Chronic hepatitis: morphology and nomenclature. *Mod Pathol* 1994; 7: 690-713.
8. Arista-Nasr J, Pichardo-Bahena R, Castaneda B, Lisker M, Keirns C. Hepatitis C: a disease with a wide morphological spectrum? *J Clin Gastroenterol* 1996; 22: 121-25.
9. Knodell RG, Conrad ME, Ishak KG. Development of chronic liver disease after acute non-A non-B post-transfusion hepatitis. *Gastroenterology* 1977; 72: 902-09.
10. Dienes HP, Popper H, Arnold W, Lobeck H. Histologic observations in human hepatitis non-A non-B. *Hepatology* 1982; 2: 562-71.
11. Bianchi L, Desmet VJ, Popper H, Scheuer PJ, Aledort LM, Berk, PD. Histologic patterns of liver disease in hemophiliacs, with special reference to morphologic characteristics of non-A, non-B hepatitis. *Semin. Liver Dis* 1987; 7: 203-09.
12. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; 21: 359-62.
13. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science* 1989; 244: 362–64.
14. Bedossa P. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; 20: 15-20.
15. Scheuer PJ. Chronic hepatitis: what is activity and how should it be assessed? *Histopathology* 1997; 30: 103-05.
16. Barcena R, Sanroman AL, Del Campo S, Garcia M, Moreno A, De Vicente E, Candela A. Posttransplant liver granulomatosis associated with hepatitis C? *Transplantation* 1998; 65: 1494-95.
17. Emile JF, Sebagh M, Feray C, David F, Reynes M. The presence of epithelioid granulomas in hepatitis C virus-related cirrhosis. *Hum Pathol* 1993; 24: 1095-97.