LEADING ARTICLE

HEPATIC GRANULOMAS

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Hepatic granulomas are not uncommon histology findings being present in 3 to 10 percent of liver biopsies[1]. While there are diverse causes of hepatic granulomas, the hepatic lesions are remarkably similar consisting basically of epithelioid cells with surrounding lymphocytes. Multinucleated giant cell, caseation and necrosis may be present. Infrequently, hepatic granulomas may show distinctive features of the underlying aetiology which includes presence of acid-fast bacilli in tuberculosis, ova in schistosomiasis, larvae and eosinophils in visceral larva migrans. For the great majority of cases, identification of their aetiologies was seldom possible on histological grounds alone. Further investigations such as serology, staining and culture of the organism, skin test coupled with clinical findings are needed to determine the underlying aetiology of hepatic granulomas.

In most series from the US and Europe, sarcoidosis and tuberculosis are the two commonest causes of hepatic granulomas[2] although the list of possible causes has been rapidly proliferating. Sarcoidosis is distinctly rare in Southeast Asia[3]. Hepatic granulomas associated with tuberculosis is most commonly seen and in miliary tuberculosis, extrapulmonary tuberculosis, and less commonly in acute or chronic pulmonary tuberculosis. Tuberculoma and primary tuberculosis of the liver are rare and are known to be associated with hepatic granulomas. In many series, acid-fast bacilli are infrequently seen. Korn et al[4] found granulomas in 24 or 30 liver biopsies of patients with extrapulmonary tuberculosis although acid-fast bacilli was only noted in two. Guckian et al[5] was able to find acid-fast bacilli in only 13% of patients with hepatic granulomas of tuberculosis. In this issue, the authors reported that only two deaths occurred in patients with tuberculous hepatic granulomas, and both cases were acid-fast bacilli positive[6]. The high mortality probably reflects a greater severity of the disease in cases with positive acid-fast bacilli. Besides tuberculosis, the list of infection causing hepatic granulomas is long. A notable example is brucellosis which affects the liver in majority of cases of which over 50% has hepatic granulomas[7,8]. Worldwide helminthic infection due to schistosomiasis is undoubtedly the most prevalent cause of granulomatous liver disease.

The liver is the major organ of metabolism. The physician is primarily concerned with hepatic injury induced by adverse reaction to therapeutic agents and exposure to toxic agents. With increasing usage of drugs and chemicals, the incidence of hepatic granulomas is expected to multiply. The drugs incriminated are the anti-hypertensives (Methyldopa, Hydralazine), anti-rheumatics (Aspirin, Phenylbutazone), antibiotics (Isoniazid, Cephalaxin, Penicillin, Sulphonamide), anti-arrhythmics (Procaineamide), less commonly oral contraceptives, Allopurinol, Diazepam, Halothane, and indeed the list is ever enlarging. The actual mechanism of drug-induced granulomas is still poorly understood, but it is thought to be hypersensitivity reaction. Histologically there are no pathognomonic features of drug-induced hepatic granulomas but the presence of eosinophils in peripheral blood and in the tissue particularly if they are accompanied by plasma cells makes the diagnosis of drug-induced granulomas probable. It may be noted however that tissue eosinophilia may be observed in histoplasmosis, visceral larva migrans and granulomas associated with Hodgkin's disease.

In most series of hepatic granulomas, there is a group of cases in which the aetiology cannot be determined. It is likely that some of these cases simply reflect the inability to identify or culture the causative agent or make the proper clinico-pathologic corrections. These patients should however be thoroughly investigated and followed up. Bunim et al[2] found that in three of 55 patients with granulomatous hepatitis of unknown of aetiology, tuberculosis developed within three years. Guckian et al[9] was able to determine the aetiology in seven of 13 patients of hepatic granulomas of unknown aetiology on extended observation.

For the clinician, the "take home messages" are simple and straightforward: vigorous search for aetiology before initiating treatment. Treatment is essentially aimed at the primary disease that is thought to be causing the granulomatous hepatitis. Although there were only few reports of repeat biopsy of liver subsequent to treatment of underlying disease, it would appear that most granulomas will resolve if the offending agent is removed or treated. Therapeutic dilemma occurs when the aetiology has remained undiscovered despite extensive investigations. In some cases, particularly those

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associated with influenza, infectious mononucleosis-like syndrome as described by Eliakim[10], continued observation and symptomatic treatment is all that is required. For those with severe systemic illness, it appears justified to embark on anti-tuberculous drugs, although bearing in mind that Isoniazid, Rifampicin and Pyrazinamide are hepatotoxic and Rifampicin and Streptomycin may actually suppress non-tuberculous bacterial infection giving rise to an erroneous diagnosis. If the disease remains unabated, corticosteroid may be introduced while the search for possible underlying causes should continue.

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