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CASE REPORT

# Granulomatous Hepatitis preceding Hodgkin's Disease

(Case-Report and Review on Differential Diagnosis)

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**Granulomas are a frequent finding in various organs with a wide range of causes. Hepatic granulomas most often occur in the course of sarcoidosis or tuberculosis. However, they also may develop during Hodgkin's disease or sometimes even precede lymphoma as shown in the case of a patient presented here. Early diagnosis of Hodgkin's disease is essential, and in the case of unexplained granulomatous hepatitis it can be achieved by taking the patients history into consideration.** (Pathology Oncology Research Vol 2, No3, 177–180, 1996)

*Key words:* granuloma, granulomatous hepatitis, Hodgkin's disease

## *Introduction*

The classical epitheloid cell granuloma represents a distinct, slow reacting form of immune response to a variety of pathogens and it may develop in various organs. However, the predominant role of the reticuloendothelial system in the liver explains the frequent fnding of hepatic granulomas in local and systemic diseases. Here, we describe the case of a patient with primarily unexplained hepatic granulomas as a preceding manifestation of Hodgkin's disease. A review of granuloma pathology, classification, causes, diagnostic tools and clinical presentation of hepatic granulomas is given.

## *Case Report*

In October 1992, a 44 year old worker in a rubber factory was transfered to our clinic because of unexplained recurrent nocturnal fever for one year. Until 1989 when asthma was diagnosed and treated for the first time, he had never been seriously ill. In July 1992 he had already been hospitalized for lung embolism after phlebotrombosis of the right vena femoralis. Since then he had been treated for nine months with phenprocoumon.

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On his first admission (Oct 1992), he complained about fever up to 40°C, arthralgia, shortness of breath and thoracic pain during exercise, recurrent cramps in both legs, nycturia, frequent obstipation, disturbance of balance and forgetfulness. He had lost 20 kg of weight within 9 weeks on a diet as he stated. Erythrocyte sedimentation rate (ESR) and C reactive protein were maximally increased during fever. However, support for a rheumatic or a hematologic disease could not be established and an infectious focus was not identified serologically. Sonography showed an obviously fatty degeneration of the liver and a marginally enlarged spleen. Computed tomography (CT) scans of the chest and abdomen showed no patologic findings. Lung function test revealed moderate obstruction. Finally, glucocorticoid was prescribed and the patient was released for further follow up.

In March 1993 he was again admitted to our clinic with symptoms unchanged. Sonography revealed a coarsened liver texture and an enlarged spleen with inhomogenous areas. No lymph nodes were detected by sonography or CT. The glucocorticoid was withdrawn as the lung function had normalized.

In August 1993 the patient presented with cholestasis in another hospital. Now, the spleen was significantly enlarged by sonography, and the liver parenchyma looked altered. Histology was taken from the liver, which showed low-grade granulomatous hepatitis *(Fig.1)*. There was no sign of a lymphoma at this time.

In October 1993 several enlarged cervical lymphnodes developed. Biopsy of one of them revealed the diagnosis

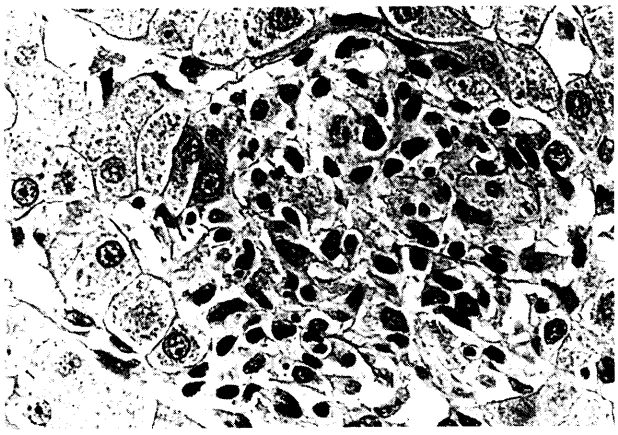

***Figure 1.*** *Lobular noncaseating granuloma with typical epitheloid cells and some lymphocytes. HE, original magnification, 500 x.*

of mixed cellularity, epithelioid cell rich subtype of Hodgkin's disease. Newly conducted CT now showed involvement not only of cervical but also thoracic and abdominal lymph nodes and spleen. With the patients consent, he was treated with 8 cycles of BEA-COPP II chemotherapy according to the German Hodgkin Study.

In June 1994, chemotherapy was finished and complete response confirmed by CT and MRI. Liver biopsy now showed only fatty degeneration with reactive inflammation.

### *Hepatic granulomas*

The term granuloma is widely used for a variety of lesions of different etiology, pathogenesis and morphology. Their common feature is the slow and localized cellular reaction to a pathogen and the presence of epitheloid cells.

Granuloma of the liver may be located at the liver hilum, subcapsular or diffusely distributed, and somtimes in the acina, close to the portal tracts or in both locations. They may be either compact or loosely structured and often contain caseous or coagulative necrosis.

The granuloma typically consist of a focal accumulation of epitheloid cells. Without the presence of epi-

***Table 1.*** **Etiology of hepatic granulomas**

| *Infections* | *Non-infectious diseases* | *Drugs and chemicals* | *Neoplasia* |
|---|---|---|---|
| *Bacteria* | *Collagen diseases* | *Drugs* | *Carcinoma* |
| Tuberculosis | SLE | Allopurinol | Gastrointestinal adenocc |
| Salmonellosis | Wegener's disease | Penicillin | |
| Brucellosis | | Sulfonamide | *Lymphoma* |
| Listeriosis | *Chronic inflammatory bowel disease* | Chinine | Hodgkin's disease |
| Granuloma inguinale | Crohn's disease | Carbamazepine | Non-Hodgkin lymphoma |
| Staphylococcus | Ulcerative colitis | Chlorpromazine | |
| | | Clofibrate | |
| *Fungi* | | Steroids | |
| Blastomycosis | *Rheumatic disease* | Diazepam | |
| Histoplasmosis | Polymyalgia rheumatica | Halothane | |
| Coccidiomycosis | | Hydrochlorothiazide | |
| Candidiasis | *Liver disease* | Methyldopa | |
| | Primary biliary | Oxyphenbutazone | |
| *Spirocheta* | cirrhosis | Phenytoin | |
| Lues | | Procainamide | |
| | *Granulomatous* | Quinidine | |
| *Protozoa* | Sarcoidosis | | |
| Leishmaniasis | | *Chemicals* | |
| Toxoplasmosis | *Inherited granulocyte disease* | Silicon | |
| | Chronic granulomatous disease | Starch | |
| *Rickettsia* | | | |
| Q fever | | | |
| *Parasitosis* | | | |
| Amoebiasis | | | |
| Helminths | | | |
| Lambliasis | | | |
| Shistosomiasis | | | |
| *Viruses* | | | |
| EBV | | | |
| CMV | | | |
| Influensa B | | | |
| HIV | | | |

*Table 2.* **Etiology of hepatic granulomas (geographical distribution)**

| | *Europe*[1] | *South Africa*[2] | | | *Saudi Arabia*[3] |
|---|---|---|---|---|---|
| | | *w* | *b* | *c* | |
| Primary biliary cirrhosis | 90 (55.2%) | 2 | 0 | 1 | |
| Sarcoidosis | 30 (18.4%) | 6 | 3 | 11 | |
| Psoriasis | 6 (3.7%) | | | | |
| Tuberculosis | 3 (1.8%) | 4 | 33 | 21 | 19 |
| Shistosomiasis | | | | | 32 |
| Brucellosis | | | | | 4 |
| Crohn's disease | 3 (1.8%) | | | | |
| Extrahepatic biliary obstruction | 2 (1.2%) | | | | |
| Chronic active hepatitis | 2 (1.2%) | | | | |
| Drug hypersensitivity | 2 (1.2%) | 2 | 0 | 2 | 2 |
| Miscellaneous | 7 (4.3%) | 2 | 1 | 6 | 2 |
| Lymphoma | | 7 | 1 | 4 | |
| Carcinoma | | 1 | 1 | 1 | |
| Idiopathic | 18 (11.0%) | 5 | 1 | 1 | |
| Total | 163 (100%) | 29 | 40 | 47 | |

1 McCluggage and Sloan, 1994; 2 Gilinski et al, 1981; 3 Satti et al, 1990.
w – whites; b – blacks; c – coloured

theloid cells the term granuloma should be avoided.[7] The transformed macrophages lose their phagocytic activity and as an epitheloid cell, they secrete interleukins and angiotensin-converting enzyme and may fuse to form syncytia or Langerhans' giant cells.

A variety of other cells like lymphocytes, plasma cells, eosinophils, Ito-cells and fibroblasts may be found as well. Fibrin, reticulum fibers and collagen can appear in the extracellular space in variable amounts. Sometimes fibrin is located around the granuloma to form a fibrin ring granuloma. At an early stage complete resolution of granulomas may occur.

Granulomas may be associated with a greater or lesser degree of nonspecific diffuse hepatitis, described as granulomatous hepatitis. Causes of hepatic granulomas are summarized in *Table 1.*[13] The prevalence of these causes differs in various geographical regions. A review covering 13 years studied 163 patients with hepatic granulomas in Northern Ireland. In 145 cases, definite clinical diagnosis was established.[17] Another review was published earlier by a South African study group *(Table 2).*[10]

In Europe, hepatic epitheloid cell granulomas are most frequently found in sarcoidosis (40-45 %), primary biliary cirrhosis (55%) and tuberculosis.[14,15,17,18] A remarable finding was that respiratory sarcoidosis frequently precedes malignant lymphoma. Between 1962 and 1971, 2544 patients with respiratory sarcoidosis were reported to the Danish Institute of Clinical Epidemiology. Malignant lymphomas occured 11 times more frequently than expected.[5]

### *Diagnostic procedures*

Granulomatous hepatitis is not associated with a specific clinical presentation or typical laboratory findings. Alkaline phosphate levels were determined in 128 patients with Hodgkin's disease.[1] The activity of the enzyme was elevated in 20 cases, but there was no correlation with hepatic pathology. Ultrasound may present diffuse, hypoechoic, small or large nodular lesions when Hodgkin's lymphoma infiltrates the liver.[11] However, unspecific hepatic involvement may only be indicated by hepatomegaly and a coarsened liver texture (as in our patient). Diagnosis has to be established histologically.

Laparoscopy with hepatic wedge biopsy is superior to deep needle biopsy. Abt et al[1] discovered noncaseating epitheloid cell granuloma in 10 patients through hepatic wedge biopsies during laparotomy, whereas 4 out of 5 deep fine needle biopsies from these patients failed to show hepatic involvement. In another study, only 5% of granulomas were found in percutaneous liver biopsies, but twice as often in samples obtained by laparoscopic biopsy or during staging laparotomy.[12]

Histologically hepatic granulomas may show some characteristic features. In these cases the underlying disease can be identified. Histiocytic granulomas for example occur in lepromatous leprosy. However, hepatic fibrin-ring granulomas are seen in Q-fever, as well as in Hodgkin's and non-Hodgkin's lymphoma, allopurinol hypersensitivity, cytomegalovirus infection, visceral leishmaniasis and hepatitis A. Demonstration of Sternberg-Reed giant cells, necessary for the definite diagnosis of Hodgkin's disease, frequently are missed in hepatic granulomas and may hinder diagnosis.[4] Positivity for CD30 antigen is useful to support Hodgkin's disease,[3] although it does not effectively differentiate Hodgkin's disease from other lymphoid tumors.[8] In any case of hepatic granulomas, associated changes in the surrounding liver (e.g. hepatitis, cholestasis, nonspecific inflammation or bile duct damage) have to be examined carefully. Staining for specific organisms, polarized microscopy for inclusions and x-ray microanalysis for gold, barium or silicon are also recommended.[7]

Some clinical parameters may support suspicion of a malignant lymphoma as the underlying cause of hepatic granulomas *(Table 3).* Patients with lymphoma-induced liver granulomas have a significantly larger spleen and

*Table 3.* **Parameters for differentiation of idiopathic from lymphoma-induced liver granulomas**

| *Parameter* | *Idiopathic* | *Lymphoma induced* |
|---|---|---|
| Age of patients (yr) | 46.7±21 | 56±12.2 |
| Spleen, diameter (cm) | 2.15±2.0 | 9.5±4.84 |
| Liver, diameter (cm) | 2.61±2.0 | 6.5±4.0 |
| Eosinophils (%) | 2.28±1.4 | 6.16±3.5 |
| Persistent fever | 3/13 patients | 5/6 patients |

liver, a higher percentage of eosinophils and a history of fever longer than 4 weeks as compared to patients with idiopathic granulomatous hepatitis.[2]

## Discussion

We presented a case with a two year history of fever, weight loss, drenching night sweats and primarily unexplained hepatic granuloma. There are many options responsible for hepatic granuloma. In some cases hepatic granulomas may even precede the clinical presentation of the underlying disease. In our case, lymphoma indicating Hodgkin's disease were not present at the time when granulomatous hepatitis was recognized. Seven months before establishing the diagnosis of lymphoma, liver texture did already appear coarsened sonographically. Provided liver histology had already been gained at that time, the patient's long history of recurrent fever as well as apparent splenomegaly 7 months before evidence of enlarged lymph nodes would have supported the diagnosis of Hodgkin's lymphoma.

The course of disease in this case emphasizes the need of early biopsy when sonography indicates hepatic abnormality. Since percutaneous deep needle biopsy is associated with high rates of failure and the sensitivity of detecting granulomas in liver biopsies depends on the size of the sample, this should be done by laparoscopy with hepatic wedge biopsy.[12]

Hepatic wedge biopsy in Hodgkin's disease may present a histology with either lymphoid infiltrates,[16] non-specifc hepatic inflammation or non-specific granulomatous disease. Hepatic granulomas are frequently seen in the absence of hepatic infiltration by Hodgkin's lymphoma.[1,21] Infiltration is a more common finding in the aggressive histological subtypes, especially in mixed cellularity forms, and it is more frequent when the spleen is involved. Patients with hepatic granulomas, however, show a significantly better overall as well as relapse-free survival.[6,19] The degree of liver involvement in Hodgkin's disease also depends on the stage of disease. It ranges from 5 to 14% at the time of diagnosis, increases to 30% during the course of the disease, and becomes as high as 60% in autopsy series.[9,20]

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