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*World J Gastroenterol* 2007 May 7; 13(17): 2504-2509
***World Journal of Gastroenterology*** ISSN 1007-9327


*CASE REPORT*

# Extrapulmonary sarcoidosis of liver and pancreas: A case report and review of literature

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Received: 2006-11-23 Accepted: 2007-02-08

## Abstract

Sarcoidosis is a chronic multisystemic granulomatous disease of unknown origin, which can involve nearly all organs. In the case of an infrequent gastrointestinal tract involvement in systemic sarcoidosis, granulomas of the liver are most commonly described while isolated pancreatic sarcoid lesions are rarely seen. We report a case of systemic sarcoidosis with exclusive extrapulmonal involvement of the liver and the pancreas in a 71-year-old white man. The diagnosis of liver involvement was confirmed by biopsy. Pancreatic surgery was needed because preoperative evaluation could not exclude pancreatic cancer and for biliary decompression. An extensive literature review of systemic sarcoidosis, focusing on reported cases with unusual presentation of sarcoidosis in the liver and the pancreas, its diagnosis, treatment, and prognosis was made.



**Key words:** Systemic; Sarcoidosis; Extrapulmonary; Liver; Pancreas

Harder H, Büchler MW, Fröhlich B, Ströbel P, Bergmann F, Neff W, Singer MV. Extrapulmonary sarcoidosis of liver and pancreas: A case report and review of literature. *World J Gastroenterol* 2007; 13(17): 2504-2509

http://www.wjgnet.com/1007-9327/13/2504.asp

## INTRODUCTION

Sarcoidosis is a chronic, multisystemic non-caseous granulomatous disease of unknown origin[1]. It can involve almost any organ, but most commonly affects the lung (90%), lymph nodes (75%), eye (25%) and skin (25%)[2]. The prevalence of systemic sarcoidosis is 1-40/100 000, being predominantly observed in Afro-Americans and in persons of Scandinavian descent, affecting mostly young adults between 20 and 40 years of age[3,4].

Involvement of the gastrointestinal tract in patients with systemic sarcoidosis is rare, and in 60%-90% of these cases, liver granulomas can be found in biopsy[2]. Exclusive liver involvement without lung disease is less frequent, documented in only about 13% of patients with systemic sarcoidosis[5]. The diagnosis of liver sarcoidosis is difficult, because symptoms or functional derangement due to involvement of the liver are uncommon in sarcoidosis[6]. If not being asymptomatic, the clinical presentation of liver sarcoidosis may be hepatosplenomegaly, increased liver enzymes, intrahepatic cholestasis and portal hypertension, as a consequence of cirrhosis due to long-standing intrahepatic cholestasis[6].

As compared to liver involvement in sarcoidosis, pancreatic sarcoidosis is rare with a prevalence in autopsy studies of 1%-5% in patients with systemic sarcoidosis[7-11]. However, pancreatic involvement has been reported even less frequently[12-26] and only isolated cases of gastrointestinal sarcoidosis exclusively in the pancreas can be found in the available literature[27-29]. Since the symptoms related to pancreatic sarcoidosis are mainly due to pancreatic tissue infiltration or ductal obstruction, the clinical presentation of pancreatic sarcoidosis resembles more common entities such as pancreatitis or pancreatic cancer[30].

We present a case of exclusive extra-pulmonary gastrointestinal sarcoidosis with hepatic and pancreatic manifestation, but without signs of other organs. In our patient, the single clinical sign for hepatic manifestation of sarcoidosis was an increase in liver enzymes. Pancreatic sarcoidosis presented as a mass in the head of the pancreas with symptoms resembling pancreatic malignancy. Pancreatic surgery was needed because the preoperative

evaluation could not exclude pancreatic cancer and for biliary decompression. We reviewed the literature on hepatic and pancreatic manifestation of sarcoidosis, its diagnosis, treatment, and prognosis.

## CASE REPORT

A 71-year-old white man was admitted to the Department of Medicine II, University Hospital of Heidelberg at Mannheim with acute upper abdominal cramps, subfebrile temperature of 37.5℃ and increasing fatigue. He had no history of regular consumption of alcohol or drugs. The patient had been treated with antimycotics (Amphomoronal®) for mycotic stomatitis, which presented as disturbance of taste and a dry mouth for about four months. Physical examination showed a red tongue and a discrete pressure pain in the left upper abdomen. About one year before the admission, the patient had had ambulatory diarrhoea and diffuse abdominal pain and cramps. He had a history of laparoscopic rectosigmoid resection and adhaesiolysis for diverticulitis two years before. Postoperative colonoscopy showed no macroscopic or histological signs for inflammatory bowel disease or specific inflammation. There was only a slight unspecific inflammation and fibrosis at the rectosigmoideal anastomosis. Symptoms could be controlled by medication with mebeverin 200 mg (Duspatal®) and butylscopolaminbromid (Buscopan®) on demand. Laboratory findings, especially pancreatic and liver enzymes were in the normal range.

Pathologic findings of the patient at admission are given in Table 1. All the other tested parameters were in the normal range, including serum amylase, aspartate aminotransferase, alanine cholinesterase and bilirubin levels and electrolytes. Tests for hepatitis A, B, and C virus were all negative. Autoantibody screens (antimitochondrial antibody (AMA), antineutrophil cytolasmic antibody (ANCA), antinuclear antibody (ANA), liver kidney microsome antibody (LKM), smooth-muscle antibody (SMA)) and serum variables of iron and copper metabolism were all in the normal range. Epstein-Barr IgM, cytomegal virus (CMV) IgG and IgM were negative. The tuberculin test was negative. The X-ray of the chest and subsequent computed tomography scan corresponded to age, and no hilar adenopathy was observed and lung capacity was normal. Electrocardiogram and ultrasound of the heart were also normal.

Upper endoscopy was macroscopically normal, and histology showed mild chronic antrum- and corpus gastritis with antral *H pylori* infection. We performed a laparoscopy to take liver biopsy. Macroscopically, there were no signs of liver cirrhosis or portal hypertension. The liver biopsy showed numerous dispersed granulomatous foci at low magnification, which at higher magnification were noncaseating and contained multiple giant cells. Plasma cells and eosinophils were not conspicuous. The reported histopathological diagnosis was "granulomatous hepatitis, compatible with sarcoidosis". Ultrasound of the abdomen showed a slightly increased echo intensity of the liver parenchyma. There was a lipomatosis of the pancreas and in the pancreatic head a hypoechogenic lesion measuring 4.7 cm × 3.2 cm × 2.9 cm was found. MRI with MRCP of the abdomen confirmed the ultrasound finding of the pancreatic head mass and demonstrated intrapancreatic stenosis of the DHC and the pancreatic duct. The former lesion did not infiltrate the surrounding vessels, with signs for lymphadenopathy but without evidence of hepatic metastasis (Figure 1).

**Table 1 Laboratory findings of the patient on admission**

| Pathologic parameters | Values | Normal range |
|---|---|---|
| Serum lipase | 1799 U/L | 114-286 U/L |
| Alkaline phosphatase (AP) | 236 U/L | 38–126 U/L |
| Gamma-glutamyl transpetidase (GGT) | 249 U/L | 0-85 U/L |
| Aminotransferase (ALAT) | 67 U/L | 0-50 U/L |
| CA 19-9 | 52 ku/L | 0-40 ku/L |
| CRP | 19 mg/L | < 5 mg/L |
| Albumin | 41.5 g/L | 60.3-71.4 g/L |
| Epstein–Barr virus (EBV) IgG | 975 U/L | 0-400 U/L |
| Angiotensin Converting Enzyme | 1.9 U/L | 8-52 U/L |

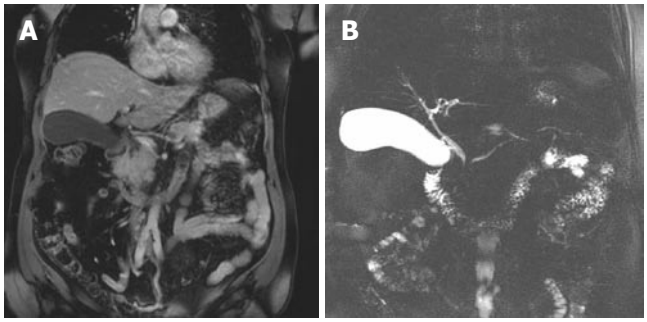


**Figure 1** Coronal T1-weighted fat-saturated MR image demonstrates pancreatic head mass measuring 4.7 × 3.2 × 2.9 cm (**A**) and MRCP shows the stenosis of the pancreatic and bile duct (**B**).

Endosonography of the pancreatic head was suspicious for pancreatic cancer. Due to the fact that the main differential diagnosis was a primary pancreatic cancer, an explorative laparotomy and partial pancreaticoduodenectomy was indicated, which was performed in the Department of Surgery, University of Heidelberg.

### *Operative procedure*

Exploration of the abdominal cavity revealed no signs of metastasis. The pancreatic mass was resected, and a pylorus preserving partial pancreaticoduodenectomy was performed with resection of the distal common bile duct. Pathologic examination of the surgical specimen revealed a firm consistency of the pancreatic head, which displayed a lobular architecture with fibrosis on the cut surface (Figure 2). The peripancreatic lymph nodes ($n$ = 28) were firm and enlarged, measuring up to 2 cm. Microscopically, the pancreatic parenchyma presented inter- and intralobular fibrosis, moderate to dense inflammatory cell infiltrates including eosinophils, numerous noncaseating granulomas composed of Langhans´giant cells, epithelioid cells and lymphocytes (Figure 3A-B). Similar granulomas were seen in the peripancreatic lymph nodes (Figure 3C). Atypical cells were not detected. The diagnosis of a noncaseating

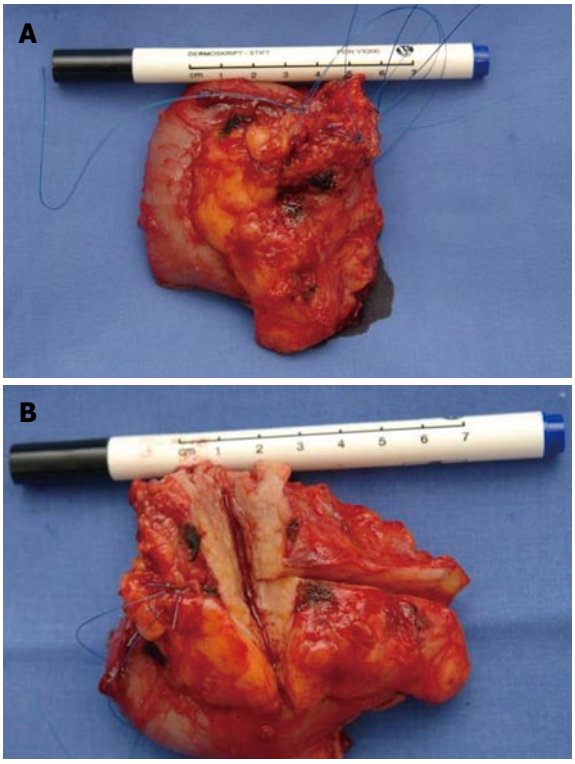


**Figure 2** Pathologic examination revealed a firm consistency of the pancreatic head. The peripancreatic lymph nodes (*n* = 28) were firm and enlarged, measuring up to 2 cm.

granulomatous pancreatitis and lymphadenitis, compatible with sarcoidosis, was established. A side to end jejuno-pancreaticostomy, a side to end hepatico-jejunostomy and a duodeno-jejunostomy with a running loop avoiding brown´s anastomosis[31] were performed.

Drains were removed on the third postoperative day when the drained fluid contained no increased amounts of amylase or lipase[32]. The postoperative course was prolonged by delayed gastric empting which was treated by placing a naso-gastric tube and i.v. administration of 250 mg of erythromycin three times a day for two days. After removing the naso-gastric tube, the patient was back to solid food in two days. The wounds were healing and staples were removed eleven days after surgery. The patient was discharged from the surgical department and admitted to the Department of Medicine II, University Hospital of Heidelberg at Mannheim on the 12th postoperative day.

### *Post-operative course*

The postoperative course was uncomplicated. A urinary tract infection was treated with antibiotics, levofloxacine 500 mg (Tavanic®) over 5 d and signs for infection vanished. The patient complained of right upper abdominal and thoracic pain and had a computer tomography (CT) of the chest and the abdomen, which showed a regular postoperative status and ruled out lung embolia. He was discharged after 4 d with discrete elevated alkaline phosphatase (AP) levels (319 U/L; normal, 38-126 U/L) and elevated gamma-glutamyl transpetidase (GGT) levels (423 U/L; normal, -85 U/L) but serum lipase levels and aminotransferase (ALAT) levels were in the normal range.

The physical and general condition of the patient was

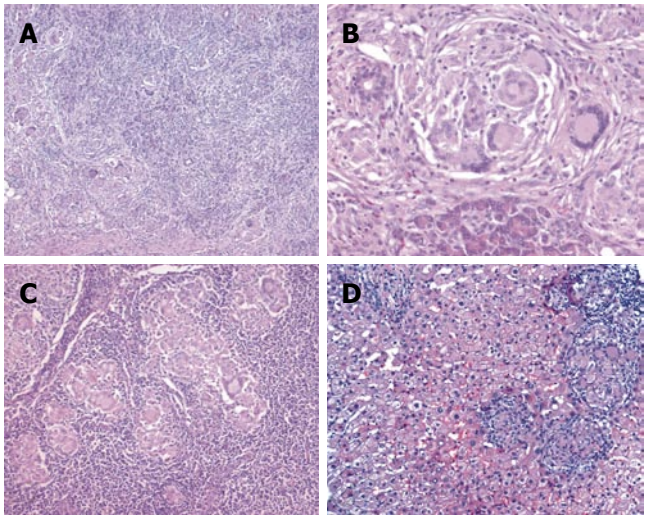


**Figure 3** Microscopic findings in the pancreas (**A-B**), peripancreatic lymph nodes (**C**) and the liver (**D**) with numerous noncaseating granulomas composed of giant cells (Langhans type), epitheloid cells, and lymphocytes. Hematoxylin & eosin staining (**A-D**). Original magnifications × 16 (**A**), × 64 (**B**), × 32 (**C**) and × 250 (**D**).

improved. He had no more sub-febrile body temperature, and had decreased alkaline phosphatase (AP) (178 U/L; normal, < 129 U/L) and gamma-glutamyl transpetidase (GGT) (162 U/L; normal, -85 U/L). In the course of observation, AP and GGT levels rose again and the patient felt sleepy so that we started a treatment with corticoids. With 40 mg prednisone daily for 8 wk and then gradually tapering the dose, the patient became asymptomatic again and liver enzymes were all in the normal range. Final diagnosis was extrapulmonary sarcoidosis of the liver and the pancreas.

## DISCUSSION

Diagnosis of systemic sarcoidosis, a multisystemic disease with unknown etiology, is based on a compatible clinical presentation involving at least two organ systems, supportive histologic evidence of noncaseating granulomas, and a reasonable exclusion of other granulomatous diseases[33,34]. Since extrapulmonary manifestation of sarcoidosis and in particular exclusive involvement of the liver and pancreas is extremely rare, few data have been published on the diagnosis, treatment and clinical course of this disease.

### *Liver involvement of sarcoidosis*

The frequency of exclusive liver involvement without lung disease in patients with systemic sarcoidosis is infrequent and seen in only 13% of patients with sarcoidosis[5]. Our patient presented with derangement of liver function. It is interesting that, in most of the patients, hepatic involvement with granulomas is asymptomatic and associated with no abnormal liver function or mild derangement[6]. Fever, as an unspecific clinical sign, correlates with hepatic manifestation of the disease. Thus, nearly 60% of patients with hepatic manifestation of sarcoidosis have fever or arthralgia, in contrast to patients without liver manifesta-tion[6]. Therefore in this case, fever constitutes an additional indication for liver biopsy[6]. Although our patient had sub-febrile body temperature, he

was asymptomatic. Since granulomas in the liver are small and preferably located in the portal space, clinical hepatic manifestations are rare. Those may include jaundice and chronic cholestasis[6,35-38], portal hypertension[39,40], or Budd Chiari syndrome[41,42]. Intrahepatic cholestasis can resemble primary biliary cirrhosis[43] or sclerosing cholangitis[44]. Sarcoidosis can also coexist with these two entities. Cirrhosis[5,45,46] and portal hypertension[39,40,45,47,48] are only found in 1% of patients with sarcoidosis. Furthermore, extrahepatic biliary tract obstruction[37] in sarcoidosis from enlarged granulomatous lymph nodes has been described, but this was not the case in our patient. Transthoracic ultrasound, CT and MRI did not raise suspicion for liver sarcoidosis. Since no reason for the derangement of liver function was found and an outpatient CT-scan had raised suspicion for liver cirrhosis, we decided to perform laparoscopic liver biopsy to confirm the diagnosis of liver sarcoidosis. It is interesting that only 20%-40% of patients with sarcoidosis had AP and GGT values increased[49,50]. Slightly increased CA 19-9 levels can be interpreted as an indicator of cholestasis[51]. Angiotensin converting enzyme (ACE), which is increased in 55% of patients with sarcoidosis, with a higher frequency in those with active disease[52,53], was not increased in our patient and serum calcium was within the normal range.

In liver biopsies, the incidence of sarcoidosis varies widely in countries and among ethnic groups. In general, granulomas are found in 4% of all liver biopsy specimens[54-56]. Of these granulomas, only 13.5%-22% are due to sarcoidosis. Histological findings of liver biopsy in our patient are given in Figure 3D. In Europe, sarcoidosis is seen in about 18% of epithelioid granulomas of the liver[54]. Others are primary biliary cirrhosis (55%) and tuberculosis or various infectious diseases[57,58]. Chronic inflammatory bowel disease is a well recognized cause of hepatic dysfunction and granulomas are found in the liver in up to 5% in this disease[59]. Epithelioid granulomas can be found in patients with psoriasis, drug hypersensitivity[60], chronic active hepatitis, extrahepatic biliary obstruction and very rarely in carcinoma[61,62] or Hodgkin disease[63-65].

### *Pancreatic involvement of sarcoidosis*

Pancreatic involvement in systemic sarcoidosis is uncommon with a prevalence in autopsy studies of 1%-5%[7-11] and an even lower prevalence in clinical series[12-26]. Only isolated cases of gastrointestinal sarcoidosis presenting exclusively in the pancreas have been reported[27-29]. Symptomatic sarcoidosis presenting as a pancreatic mass is extremely rare and only 25 cases have been reported in the literature since first described by Curran and Curran in 1950[14]. Out of these cases, 12 presented with a pancreatic mass, that in most cases was located in the head of the pancreas[14]. The remaining cases revealed a diffusely indurated nodular pancreas.

Our patient had a pancreatic mass in the head of the pancreas by ultrasound, MRI and endoscopic ultrasound. Based on imaging procedures alone, it was not possible to exclude pancreatic cancer or pancreatitis. In accordance to the literature, he had abdominal pain which is the most common symptom (66% of cases) in patients with liver sarcoidosis. He had no other frequent complaints such as weight loss (45%), jaundice (29%) and nausea/emesis (20%). Unfortunately, there is no specific test for the preoperative diagnosis of pancreatic sarcoid without the presence of more classic findings of this disease or a previous pathologic diagnosis. History of sarcoidosis before the manifestation that led to the discovery of pancreatic involvement was only present in 4 (16%) of 35 patients.

Symptoms related to the presence of pancreatic sarcoidosis originate secondary to pancreatic tissue infiltration or double duct sign due to bile stock. This is the reason why it clinically presents like pancreatitis or pancreatic cancer[30] (Figure 1). Given the inability to rule out pancreatic cancer and the dilatation of the biliary tree, our patient required surgical intervention for decompression and diagnosis. Furthermore, the usefulness of diagnostic tests in this setting is questionable and no reports exist in the literature of pancreatic sarcoidosis diagnosed by non-surgical means of biopsy, including CT or endoscopic ultrasound. Preoperative and operative findings could not exclude pancreatic cancer and therefore standard pancreaticoduodenectomy was performed. An exception to this procedure would have required a definite previous diagnosis of sarcoidosis but we had to assume that the finding of isolated granulomas found in the preoperative liver biopsy without other clinical findings for systemic sarcoidosis was not sufficient to exclude the possibility of pancreatic carcinoma and to avoid pancreatic surgery. Chronic pancreatitis was less probable because there was no anamnestic evidence and pancreatic endocrine and exocrine function was normal.

### *Treatment and prognosis*

Steroids are an important base in the treatment of pulmonary sarcoidosis. Nevertheless, the exact time point of treatment, dosage, and benefits versus side effects are still controversial[5,66-72]. Because sarcoidosis has such varied manifestations, severity, and course, there have been no valid prospective placebo-controlled treatment trials. Prolonged length of observation and a large number of patients are required[33] to prove the effectiveness of treatment strategies. In asymptomatic patients or those with mild lung disease, the side effects of systemic steroids often exceed the benefits of treatment[6], and the disease may spontaneously remit. In the literature, there are only a few reports on treatment of liver sarcoidosis[5,73,74]. These cases demonstrate that liver function may improve even though liver granulomas may persist on histology. Early steroid treatment does not preclude the development of intrahepatic cholestasis or development of portal hypertension. Therefore, the role of liver biopsies seems undoubted not only in diagnosis, but also in continued disease. In patients where liver function tests were deranged for a time, corticosteroids have been used as a first line treatment[75].

A more recent publication[5] summarizes cases of hepatic dysfunction complicated with lung disease and significant liver involvement presenting independent of pulmonary sarcoid (23 of 180 patients with a follow-up of two years (13%). Sixty-three patients were treated with corticosteroids based on current protocols 30-40

mg of prednisone daily for 8-12 wk and then gradual tapering of the dose to 10-20 mg over a period of 6-12 mo, to establish the minimal effective dose[4]. In the above-mentioned study, approximately one third had a complete clinical response, one-third a partial response and one-third no response. This study, providing the first comprehensive review of liver involvement in sarcoidosis, suggests that hepatic sarcoidosis can be a serious and rapidly progressive disease[76]. The authors conclude that in case of chronic liver disease treatment should be started irrespective of the absence of pulmonary or other extrahepatic manifestations.

Alternatives to steroids have been tried, being primarily limited to steroid refractory cases. Methotrexate[5,73,76-78] has shown the greatest promise of these alternative agents, but again, data are limited. In cases of hepatic cholestasis, ursodeoxycholic acid may be beneficial[79]. Organ transplantation is often the only treatment modality in advanced sarcoidosis of the liver. Cyclosporine has been used successfully in a cohort of nine patients transplanted for sarcoidosis with no evidence of disease recurrence. Nevertheless, recurrence of disease in the allograft has been reported in a previous case report[80-82].

No general conclusion can be drawn on medical treatment of pancreatic sarcoidosis. Up to now, in the literature, 25 cases of pancreatic sarcoidosis presenting as a pancreatic mass have been reported. Among 18 patients, treatment regimens were compared, 6 patients improved spontaneously without corticosteroids and 10 with prednisone treatment[28].

In summary, we report a case of systemic sarcoidosis with extrapulmonal involvement of the liver and the pancreas. Pancreatic surgery was required to exclude pancreatic cancer. Liver biopsies are a valuable tool for diagnosis and also for disease monitoring in patients with liver sarcoidosis. The prognosis of mild disease and pancreatic involvement is good, with high spontaneous remission rates. The exact time point of treatment, dosage, and benefits versus side effects for corticoids in extrapulmonary sarcoidosis are still discussed controversially.

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