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Clinical Characteristics and Outcome of Hepatic Sarcoidosis: A Population-Based Study 1976–2013

Patompong Ungprasert, MD[1,2,*], **Cynthia S. Crowson, MS**[1,3], **Douglas A. Simonetto, MD, PhD**[4], and **Eric L. Matteson, MD, MPH**[1,5]

[1]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA [2]Division of Rheumatology, Department of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [3]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA [5]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA

Abstract

Objectives—Data on clinical manifestations and outcome of hepatic sarcoidosis are scarce. This study aimed to use a population-based cohort of patients with incident sarcoidosis to better describe the characteristics of hepatic sarcoidosis.

Methods—A cohort of incident cases of sarcoidosis in Olmsted County, Minnesota, United States from 1976 to 2013 was identified from the database. Diagnosis was verified by individual medical record review. Confirmed cases of sarcoidosis were then reviewed for liver involvement. Data on clinical manifestations, imaging study, liver biochemical tests, treatment and outcome were collected. Cumulative incidence of cirrhosis adjusted for the competing risk of death was estimated.

Results—A total of 345 cases of incident sarcoidosis were identified. Of these, 19 cases (6%) had liver involvement (mean age 46.1 years, 53% female and 79% Caucasian). Most patients had

[*]Corresponding author; P.U.: P.Ungprasert@gmail.com; Ungprasert.Patompong@mayo.edu, Division of Rheumatology, Mayo Clinic, 200 First avenue SW, Rochester, MN 55905, USA, Tel 507-284-8450; Fax 507-284-0564.

Guarantor of the article:
Patompong Ungprasert, MD

Specific author contributions:
Patompong Ungprasert: 1. Conception and design 2. Acquisition and interpretation of data 3. Drafting of the manuscript 4. Statistical analysis 5. Approval of the final draft
Cynthia S. Crowson: 1. Conception and design 2. Analysis and interpretation of data 3. Critical revision of the manuscript for important intellectual content 4. Statistical analysis 5. Approval of the final draft
Douglas A. Simonetto: 1. Conception and design 2. Acquisition and interpretation of data 3. Critical revision of the manuscript for important intellectual content 3. Approval of the final draft
Eric L. Matteson: 1. Conception and design 2. Acquisition and interpretation of data 3. Critical revision of the manuscript for important intellectual content 4. Statistical analysis 5. Approval of the final draft

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asymptomatic liver disease and were discovered in pursuit of abnormal biochemical tests and imaging studies. Alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) were elevated in the majority of patients (88% and 90%, respectively). Elevated transaminases were less common and less severe. About half of patients had abnormal imaging study with hypodense nodular lesions being the most common abnormality (6 patients) followed by hepatomegaly (3 patients). Liver biopsy revealed non-caseating granuloma in 88% (14 of 16 patients). A total of 4 patients developed cirrhosis.

Conclusions—Involvement of the liver by sarcoidosis was seen in 6% of patients with sarcoidosis. The majority of patients were asymptomatic. Elevated ALP and GGT were the most common abnormal biochemical tests. Liver biopsy revealed non-caseating granuloma in almost all cases. Cirrhosis was seen in a significant number of patients. Generalizability of the observations to other populations may be limited as the studied population was predominantly Caucasian. The prevalence of liver disease may be higher in more diverse populations.

Keywords

Sarcoidosis; Hepatic sarcoidosis; Epidemiology

Introduction

Sarcoidosis is a chronic granulomatous inflammatory disease of unclear etiology. The characteristic histological finding of sarcoid granuloma consists of epithelioid cells and multinucleated cells without area of necrosis, unlike caseating granuloma of tuberculosis (1). It has been estimated that 70,000 – 80,000 new cases of sarcoidosis are diagnosed in the United States annually with a significant variation across regions and ethnic groups (2, 3).

Sarcoidosis can virtually affect any organ, with lung and mediastinal lymph node being the most frequently affected sites (4). Liver involvement by sarcoidosis is relatively common with prevalence ranging from 5% to 30% in antemortem cohort studies (5–9) and as high as 70% in an autopsy study (10). However, clinical characteristics and outcome of hepatic sarcoidosis are not well-defined as most available studies used referral-based cohorts which may not reflect the disease as it occurs in the community. This study aimed to use the data from a previously identified cohort of patients with incident sarcoidosis in Olmsted County, Minnesota (MN), United States (11) to better characterize the epidemiology, clinical findings and course of hepatic sarcoidosis.

Methods

Participants and study design

This is a retrospective cohort study that utilized the medical record-linkage system of the Rochester Epidemiology Project (REP) to identify potential cases of sarcoidosis from 1976 to 2013 using diagnosis codes related to sarcoid, sarcoidosis and non-caseating granuloma. The REP medical record-linkage system provides comprehensive access to medical records of all residents of Olmsted County, MN from all local health care providers which include the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes and the few private practitioners. This approach allows identification of virtually all

clinically recognized cases of sarcoidosis in the community. Detailed methodology and clinical application of the REP medical record-linkage system has previously been described (12).

Medical records of those potential cases with sarcoidosis related diagnostic codes were individually reviewed. The diagnosis of sarcoidosis required a diagnosis made by physicians who evaluated the patient supported by presence of non-caseating granuloma on histopathology, radiologic features of intrathoracic sarcoidosis, compatible clinical presentation and exclusion of other granulomatous diseases such as tuberculosis and fungal infection. The only exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only the presence of symmetric bilateral hilar adenopathy on chest x-ray or computerized tomography without any other identifiable causes. Isolated granulomatous disease of a specific organ without intra-thoracic sarcoidosis was also included if other possible causes of granulomatous inflammation were excluded. Prevalent cases (i.e., cases with sarcoidosis prior to residency in Olmsted County) were not included.

Confirmed cases of sarcoidosis were then reviewed for liver involvement. If the patient had systemic sarcoidosis (pulmonary sarcoidosis with or without involvement of other organs), liver involvement by sarcoidosis was defined as presence of hypodense nodular lesions on liver imaging study or presence of abnormal liver biochemical tests without other identifiable causes (such as drugs, viral hepatitis, autoimmune liver diseases, fatty liver and significant alcohol consumption). Histopathological confirmation was not necessary in this situation. However, if the patient did not have systemic sarcoidosis, diagnosis of isolated hepatic sarcoidosis required the presence of non-caseating granuloma on biopsy and exclusion of other causes of granulomatous hepatitis (such as tuberculosis, brucellosis, drugs and primary biliary cirrhosis).

Data on demographic characteristics, clinical manifestations related to hepatic sarcoidosis, imaging study of the liver, liver biochemical tests at baseline as well as at last follow-up visit, treatment and outcome were collected. Follow-up was continued until death, migration out of system or February 1, 2017. This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee. The need for inform consent was waived.

Statistical analysis

Descriptive statistics (percentages, means, etc.) were used to summarize the characteristics of the cohort. The cumulative incidence of cirrhosis adjusted for the competing risk of death was estimated (13). These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. However, patients who died before experiencing cirrhosis are appropriately accounted for to avoid overestimation of the rate of occurrence of the events of interest, which can occur if such subjects are simply censored at death. Mortality rates were estimated using the Kaplan-Meier method and compared to expected mortality for persons of the same age, sex and calendar year estimated using Minnesota population life tables. The standardized mortality rate (SMR) was estimated as

the ratio of the observed and expected number of deaths. SMR 95 % confidence intervals were calculated assuming that the expected rates are fixed and the observed rates followed a Poisson distribution. A Cox model including the entire sarcoidosis cohort with liver involvement modeled as a time-dependent covariate was used to examine whether liver involvement was a prognostic factor for death among patients with sarcoidosis after adjustment for age, sex and calendar year of sarcoidosis diagnosis. A P-value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Out of 345 incidental cases of sarcoidosis, 19 cases (6%) had liver involvement (mean age 46.1 years, 53% female and 79% Caucasian). Median time from sarcoidosis diagnosis to hepatic involvement was 0.0 months (range: −3.3, 78.5 months). Median length of follow-up from diagnosis of hepatic sarcoidosis to last follow-up was 10.1 years (range: 0.0, 20.9 years). Most patients were asymptomatic from liver disease. Liver involvement was discovered in evaluation of abnormal biochemical tests/imaging study (12 cases; 63%) or at autopsy (3 cases; 16%). Most patients were diagnosed on the basis of positive liver biopsy and cholestatic biochemical liver tests (7 cases) followed by positive imaging study and cholestatic biochemical liver tests (4 cases); positive imaging study, liver biopsy and cholestatic biochemical liver tests (4 cases); positive liver biopsy alone (3 cases) and positive imaging study alone (1 case). Most cases of hepatic sarcoidosis occurred in conjunction with pulmonary sarcoidosis (16 cases). Only 3 cases had hepatic sarcoidosis in isolation without intra-thoracic disease.

At diagnosis of liver disease, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were elevated in the majority of patients (15 of 17 tested patients (88%) and 9 of 10 tested patients (90%), respectively). The mean of ALP was 394.6 international units (IU)/L (upper normal limit 118 IU/L [UNL]; 3.3 times UNL) and the mean of GGT was 175.1 IU/L (UNL 29 IU/L; 6.0 times UNL). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated in 10 patients (71% of tested patients) and 9 patients (53% of tested patients), respectively. The mean of ALT was 68.3 IU/L (UNL 45 IU/L; 1.5 times UNL) and the mean of AST was 50.9 IU/L (UNL 43 IU/L; 1.2 times UNL). Hyperbilirubinemia was seen in only 2 patients (10%). Mean albumin was 4.0 g/dL. No prolongation of prothrombin time test was observed.

Imaging studies (ultrasonography or computerized tomography of the liver) were obtained at diagnosis of hepatic sarcoidosis in 16 patients. It was normal in nearly half (9) of the cases. The most common radiographic abnormality was hypodense nodular lesions (6 patients) followed by hepatomegaly (3 patients). Liver biopsy was performed in 16 patients; non-caseating granulomas were identified in 14 cases (88%).

Anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver kidney microsome type 1 and anti-neutrophil cytoplasmic antibody were obtained in 10, 7, 3 and 5 patients,

respectively. None of these tests were positive. Anti-nuclear antibody was tested in 10 patients and was present in 4 cases (40 %). Angiotensin converting enzyme (ACE) was tested in 15 patients and was elevated in 9 of them (60%). Baseline characteristics, liver biochemical tests, pathology and imaging study of patients in this cohort are summarized in table 1.

Treatment

Oral glucocorticoids were the most commonly used medications in management of the hepatic disease. A total of 11 patients with hepatic sarcoidosis were exposed to oral glucocorticoids at some point during follow-up which corresponded to estimated 30 year cumulative incidence of ever using this medication of 66.5% (95% confidence interval [CI], 32.5– 83.4). A small portion of patients were exposed to non-biologic immunosuppressive agents. Two patients received methotrexate, corresponding to an estimated 30 year cumulative incidence of 12.5% [95% CI, 0.0 – 27.3]. One patient was treated with hydroxychloroquine (estimated 30 year cumulative incidence 6.2% [95% CI, 0.0 – 17.4]), and one patient was treated with a tumor necrosis factor alpha inhibitor (estimated 30 year cumulative incidence 6.7% [0.0 – 18.5]).

Outcome

A total of 4 patients in this cohort developed liver cirrhosis. Cirrhosis was found at diagnosis of hepatic sarcoidosis in 2 patients, while the other 2 patients developed cirrhosis during follow-up (1 at 1 year and 1 at 12 years after diagnosis of hepatic sarcoidosis). All patients with cirrhosis had radiographic evidence of cirrhosis. Histopathological confirmation was performed in 2 patients. Signs and symptoms of portal hypertension (including ascites and esophageal varices) were observed in 3 of these 4 patients with cirrhosis. No case of portal hypertension without cirrhosis was observed. None of the patients in this cohort developed hepatocellular carcinoma or underwent liver transplantation.

Improvement of liver biochemical tests was observed. Mean of ALT, AST and ALP at the last test were lower compared to the values at diagnosis with the mean of 49.9 IU/L (1.1 times UNL), 36.8 IU/L (0.86 times UNL) and 148.6 IU/L (1.26 times UNL), respectively (data on GGT is not available as only 1 patient had GGT after the initial diagnosis). Of those 10 patients who had elevated ALT at diagnosis, 6 patients had normalized ALT at the last follow-up, 2 had lower ALT but not to the normal range and 2 did not have any follow-up ALT. Of those 9 patients who had elevated AST at diagnosis, 4 patients had normalized AST at the last follow-up, 4 had lower AST at the last follow-up but not to the normal range and 1 did not have any follow-up AST. Normalization of ALP occurred in 8 of 15 patients with elevated ALP at diagnosis, 5 had lower ALP at the last follow-up but not to the normal range, 1 had slightly higher ALP and 1 did not have any follow-up ALP.

Oral glucocorticoids were used to treat 11 of the 16 patients whose hepatic sarcoidosis was not found at autopsy, and several were also treated with antimetabolite immunosuppressive agents. The ALP was elevated at diagnosis in 10 of the glucocorticoids-treated patients. At the last follow-up, 6 patients had normalized ALP while 3 patients had lower ALP but not to the normal range. Follow-up ALP was not available for 1 patient. All of the 5 patients who

did not receive treatment with oral glucocorticoids or immunosuppressive agents, 5 had elevated ALP at diagnosis. At last follow-up, 2 of these patients had normalized ALP, 2 patients had lower ALP but not to the normal range and 1 patient had a higher ALP. Decisions regarding treatment with oral glucocorticoids and immunosuppressive agents were primarily guided by the severity and activity of non-hepatic sarcoidosis in more than half of patients (7 of 11). Clinical characteristics, laboratory investigations and clinical outcomes of individual patients are provided in table 2.

Follow-up imaging was obtained in all 6 patients with hypodense nodular lesions in the liver, and resolution of the hepatic nodules was observed in all but 1 patient.

Of 17 patients whose diagnosis of hepatic sarcoidosis were not made at autopsy, 3 died during follow-up (standardized mortality ratio of 2.05 [95% CI, 0.42 – 6.00, p=0.20]). Liver involvement was a significant prognostic factor for death among patients with sarcoidosis in this cohort, with hazard ratio of 5.79 (95% CI, 2.05 −16.36, p<0.001 adjusted for age, sex and calendar year of sarcoidosis diagnosis)

Discussion

This is the first population-based study using comprehensive individual medical record review to describe the epidemiology, clinical characteristics and outcome of hepatic sarcoidosis. Compared to previous referral-based cohort studies (5–9) that reported a prevalence of hepatic involvement by sarcoidosis between 5% and 30%, the prevalence in this cohort was at the lower range. The lower frequency probably reflects the population-based nature of the study that may capture a more complete spectrum of sarcoidosis, including those with milder disease without extensive extra-thoracic involvement, unlike referral-based cohorts that may overestimate the prevalence of patients with more severe disease as a result of referral bias. Nonetheless, a post-mortem study from Japan found that 70% of patients with sarcoidosis had evidence of hepatic involvement at autopsy (10) which is considerably higher than the prevalence from ante-mortem cohorts, suggesting that liver involvement by sarcoidosis is generally under-recognized in clinical practice.

The relatively symptomless nature of hepatic sarcoidosis could be responsible for this discrepancy in prevalence estimates of hepatic involvement. The majority of patients in the current study cohort did not have any symptoms from their liver disease, similar to other studies that observed symptoms in only 25% to 40% of patients (15, 16). Only 4 patients in this study (20%) had abdominal pain and only 2 patients (10%) were found to have hepatomegaly on physical examination. No patient presented with cholestatic symptoms (pruritus and/or jaundice). Thus, most cases of hepatic sarcoidosis are identified based upon evaluation of liver biochemical tests and imaging studies, which are generally the crucial first step in recognizing and diagnosing hepatic sarcoidosis. Whether routine screening for hepatic involvement in patients with sarcoidosis using liver biochemical tests and/or imaging study should be recommended requires further investigation for cost-effectiveness analysis.

Ethnic background may also play a significant role in the lower prevalence of hepatic involvement identified in this predominantly Caucasian cohort. Clinical manifestations of

sarcoidosis vary across ethnic groups (2, 3, 14). In fact, a study that prospectively recruited patients with newly-diagnosed sarcoidosis from 10 centers across the United States found that hepatic involvement was approximately 3 times more common among African-Americans than Caucasians (17).

The most commonly abnormal biochemical liver tests were elevated ALP and GGT, likely reflecting the infiltrative nature of sarcoidosis. On average, these tests were elevated more than 3 times the UNL. Elevated AST and ALT were also found, but are less frequent and less severe than ALP/GGT elevations, with means of less than 2 times of UNL. These findings suggest that other causes of hepatic injury should be explored among patients with sarcoidosis who have significantly elevated serum aminotransferase with normal or minimally elevated ALP/GGT. Hyperbilirubinemia was uncommon and liver synthetic function was preserved in all patients. These observations are in line with data from previous cohort (16, 18–20). ACE was elevated in only 60% of tested patients which suggest its poor sensitivity for diagnosis of hepatic sarcoidosis, similar to its poor performance for diagnosis of systemic sarcoidosis (21, 22).

Only approximately half of patients had an abnormal imaging study. The most common abnormality in this cohort was hypodense nodular lesions (35%) followed by hepatomegaly (18%). The frequency of hepatic nodules varies considerably among studies, ranging from 5% to 38%, depending on the underlying population and methodology (19, 20, 23, 24). On the other hand, liver biopsy findings of non-caseating granuloma, detected in 14 out of 16 biopsies (88%) have higher sensitivity for the diagnosis of hepatic sarcoidosis. The high sensitivity of liver biopsy has been consistently demonstrated in several cohorts (15, 16, 18). Therefore, negative imaging study does not exclude hepatic sarcoidosis, and liver biopsy should be performed if the clinical suspicion remains high.

At diagnosis of hepatic sarcoidosis, 2 patients (10%) were also found to have cirrhosis. This frequency is similar to previous studies that reported the prevalence of cirrhosis at diagnosis of hepatic sarcoidosis of 6% to 24% (9, 15, 16, 20). This observation underscores the relatively symptomless nature of hepatic sarcoidosis and that the disease may not be recognized until organ failure or death occur.

Medical treatment is generally reserved for patients with more severe disease and observation is usually recommended for patients with only mildly elevated liver enzymes (25, 26). This approach is partially based on the fact that there is no randomized controlled study to confirm the efficacy and long-term benefit of glucocorticoids and/or other immunosuppressive agents for treatment of hepatic sarcoidosis. Glucocorticoids are generally considered as the first line therapy (and were the most commonly used medications in this cohort) based on low quality data from retrospective studies which were at risk of selection bias (9, 26, 27). Interestingly, more than half of patients in this cohort received glucocorticoid therapy, reflecting the practice pattern of healthcare-providers in this community.

The major strength of this study is the population-based design that reflects the true spectrum of the disease in the community with minimal selection bias, unlike hospital-based

cohorts. The diagnosis of both sarcoidosis and cirrhosis was verified by individual medical record review which minimized the likelihood of disease misclassification. The long duration of follow-up allows capture of events of interest occurring during long-term follow up. This is of particular importance for study of hepatic sarcoidosis as the outcome of interest (cirrhosis) could happen years after the diagnosis.

The major study limitations are inherent to the retrospective design. Clinical information was not obtained and recorded according to a defined protocol. Thus, some of the pertinent data were not available. Liver imaging study and biochemical tests were obtained at physician discretion without a standard protocol which could introduce elements of surveillance and selection bias. Generalizability of the observations to other populations may be limited as clinical manifestation of sarcoidosis varies among ethnic groups (2, 3) and the population of Olmsted County as well is predominately of Northern European ancestry. In addition, Olmsted County has a higher proportion of workers in the healthcare industry which may result in a different pattern of hepatic sarcoidosis detection, as patients may have better access to healthcare service.

Conclusion

Involvement of the liver by sarcoidosis was seen in 6% of patients with sarcoidosis in this cohort. The majority of them were asymptomatic. Elevated ALP and GGT were the most common abnormal biochemical tests. Liver biopsy revealed non-caseating granuloma in almost all cases.

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References

1. Yee AM. Sarcoidosis: Rheumatology perspective. Best Pract Res Clin Rheumatol. 2016; 30:334–56. [PubMed: 27886804]
2. Rybicki BA, Major M, Popovich J Jr, et al. Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am J Epidemiol. 1997; 145:234–41. [PubMed: 9012596]
3. Dumas O, Abramovitz L, Wiley AS, et al. Epidemiology of sarcoidosis in a prospective cohort of U.S. women. Ann Am Thorac Soc. 2016; 13:67–71. [PubMed: 26501211]
4. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J. 1999; 14:735–7. [PubMed: 10573213]
5. Judson MA. Hepatic, splenic, and gastrointestinal involvement with sarcoidosis. Semin Respir Crit Care Med. 2002; 23:529–41. [PubMed: 16088648]

6. Morimoto T, Azuma A, Abe S, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J. 2008; 31:372–9. [PubMed: 17959635]
7. Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. Sarcoidosis Vasc Diffuse Lung Dis. 2012; 29:119–27. [PubMed: 23461074]
8. Cozier YC, Berman JS, Palmer JR, et al. Sarcoidosis in black women in the United States: Data from the black women's health study. Chest. 2011; 139:144–50. [PubMed: 20595459]
9. Kennedy PTF, Zakaria N, Modawi SB, et al. Natural history of hepatic sarcoidosis and its response to treatment. Euro J Gastroenterol Hepatol. 2006; 18:721–6.
10. Iwai K, Oka H. Sarcoidosis: report of ten autopsy cases in Japan. Am Rev Respir Dis. 1964; 90:612–22. [PubMed: 14221674]
11. Ungprasert P, Carmona EM, Utz JP, et al. Epidemiology of sarcoidosis 1946–2013: A population-based study. Mayo Clin Proc. 2016; 91:183–8. [PubMed: 26727158]
12. Rocca WA, Yawn BP, St Sauver JL, et al. History of the Rochester Epidemiology Project: Half a century of medical records linkage in a U.S. population. Mayo Clin Proc. 2012; 87:1202–13. [PubMed: 23199802]
13. Gooley TA, Leisenring W, Crowley J, et al. Estimation of impairment probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18:695–706. [PubMed: 10204198]
14. Pietinalho A, Ohmichi M, Lofroos AB, et al. The prognosis of pulmonary sarcoidosis in Finlnad and Hokkaido, Japan. A comparative five-year of biopsy-proven cases. Sarcoidosis Vasc Diffuse Lung Dis. 2000; 17:158–66. [PubMed: 10957764]
15. Devaney K, Goodman ZD, Epstein MS, et al. Hepatic sarcoidosis: Clinicopathologic features in 100 patients. Am J Surg Pathol. 1993; 17:1272–80. [PubMed: 8238735]
16. Bihari C, Rastogi A, Kumar N, et al. Hepatic sarcoidosis: Clinico-pathological characterization of symptomatic cases. Acta Gastroenterol Belg. 2015; 78:306–13. [PubMed: 26448412]
17. Baughman RP, Teirstein AS, Judson MA, et al. Case Control Etiologic Study of Sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001; 164:1885–9. [PubMed: 11734441]
18. Ennaifer R, Ayadi S, Romdhane H, et al. Hepatic sarcoidosis: a case series. Pan Afr Med J. 2016; 24:209. [PubMed: 27795804]
19. Karagiannidis A, Karavalaki M, Koulaouzidis A. Hepatic sarcoidosis. Ann Hepatol. 2006; 5:251–6. [PubMed: 17151576]
20. Judson MA. Hepatic, splenic, and gastrointestinal involvement of sarcoidosis. Semin Respir Cirt Care Med. 2002; 23:529–41.
21. Ungprasert P, Carmona EM, Crowson CS, et al. Diagnosis utility of angiotensin-converting enzyme in sarcoidosis: a population-based study. Lung. 2016; 194:91–5. [PubMed: 26563332]
22. Bunting PS, Szalai JP, Katic M. Diagnosis aspects of angiotensin-converting enzyme in pulmonary sarcoidosis. Clin Biochem. 1987; 20:213–9. [PubMed: 2820616]
23. Warshauer DM, Dumbleton SA, Molina PL, et al. Abdominal CT findings in sarcoidosis: Radiologic and clinical correlation. Radiology. 1994; 192:93–8. [PubMed: 8208972]
24. Britt AR, Francis IR, Glazer GM, et al. Sarcoidosis: Abdominal manifestation at CT. Radiology. 1991; 178:91–4. [PubMed: 1984330]
25. Cremers JP, Drent M, Baughman RP, et al. Therapeutic approach of hepatic sarcoidosis. Curr Opin Pulm Med. 2012; 18:472–82. [PubMed: 22617809]
26. Syed U, Alkhawam H, Bakhit M, et al. Hepatic sarcoidosis: pathogenesis, clinical context, and treatment options. Scan J Gastroenterol. 2016; 51:1025–30.
27. Vatti R, Sharma OP. Course of asymptomatic liver involvement in sarcoidosis: the role of therapy in selected cases. Sarcoidosis Vasc Diff Lung Dis. 1997; 14:73–6.

Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- Data on characteristics and outcome hepatic sarcoidosis varied considerably among previous studies.
- All of the previously published studies are referral-based studies which may have selection bias.

2. WHAT IS NEW HERE

- Prevalence of hepatic involvement by sarcoidosis in this population-based cohort is 6%.
- Alkaline phosphatase and gamma-glutamyl transpeptidase were elevated in the majority of patients.
- About half of patients had abnormal imaging studies, with hypodense nodular lesions being the most common abnormality.

Table 1

Demographics, clinical characteristics and laboratory investigations of patients with hepatic sarcoidosis

Demographics		
Age at diagnosis (years), mean ± SD	46.1 ± 18.0	
Female sex (No. [%])	10 (53)	
Ethnicity (No. [%])		
White	15 (79)	
African-American	1 (5)	
Native American	1 (5)	
Other	2 (11)	
Months from sarcoidosis diagnosis to hepatic involvement, median (range)	0.0 (−3.3, 78.5)	
Length of follow-up (years), median (range)	10.1 (0.0, 20.9)	
Clinical characteristics		
Clinical presentations (No. [%])		
No sign and symptom	15 (79)	
Abdominal pain	4 (21)	
Hepatomegaly	2 (11)	
Jaundice	0 (0)	
Pruritus	0 (0)	
Imaging study at diagnosis of liver involvement (No. [%])		
Number of tested patients	16	
No abnormality	7 (44)	
Hypodense nodular lesions	6 (38)	
Hepatomegaly	3 (19)	
Splenomegaly	2 (13)	
Cirrhosis	2 (13)	
Ascites	0 (0)	
Liver biopsy (No. [%])		
Number of tested patients	16	
Presence of non-caseating granuloma	14 (88)	
ACE at diagnosis of liver involvement (No. [%])		
Number of tested patients	15	
Number of patients with elevated ACE level	9 (60%)	
Liver biochemical tests at diagnosis of liver involvement	Number elevated / Number of tested patients (%)	Mean ± SD
AST	9/17 (53)	50.9 ± 22.5 IU/L
ALT	10/14 (71)	68.3 ± 37.1 IU/L

ALP	15/17 (88)	394.6 ± 390.9 IU/L
GGT	9/10 (90)	175.1 ± 101.2 IU/L
Total bilirubin	2/16 (13)	0.8 ± 0.5 mg/dL
Direct bilirubin	2/15 (13)	0.2 ± 0.1 mg/dL
Albumin *	0/16 (0)	4.0 ± 0.8 g/dL
INR **	0/14 (0)	1.0 ± 0.1
Serology at diagnosis of liver involvement	Number positive / Number of tested patients (%)	
ANA	4/10 (40)	
AMA	0/10 (0)	
ASMA	0/7 (0)	
MPO-ANCA	0/5 (0)	
PR3-ANCA	0/5 (0)	
Anti-LKM-1	0/3 (0)	

* Number of patients below lower normal limit

** Elevated of more than or equal to 1.4

SD, standard deviation; IQR, interquartile range; ACE, angiotensin converting enzyme; No., number; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMA, anti-mitochondrial antibody, ASMA, anti-smooth muscle antibody; anti-LKM-1, anti-liver kidney microsome type 1; ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; IU, international unit, L, litre; dL, deciliter; mg, milligram; g, gram

Table 2

Clinical characteristics, treatment and complications of 19 patients with hepatic sarcoidosis

Case	Age (years)	Sex	Liver signs and symptoms	Other involved organs	Liver imaging at diagnosis*	Liver biopsy	Treatment	At diagnosis				At last follow up				Presence of cirrhosis
								AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (mg/dL)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (mg/dL)	
1	70	F	None	Lung and skin	Low-attenuation nodules	Not performed	Prednisone (primarily for lung disease)	51	77	420	0.3	22	26	168	0.6	Yes (3 years after diagnosis of hepatic sarcoidosis) Diagnosed by imaging study and liver chemistry test
2	58	M	None	Lung, small bowel and pelvic lymph node	Low-attenuation nodules	Not performed	Prednisone (primarily for lung disease and hyper-calcemia)	40	58	621	0.9	64	32	93	3.7	Yes (12 years after diagnosis of hepatic sarcoidosis) Diagnosed by imaging study, liver chemistry test and signs of chronic liver disease
3	73	M	None	Lung	Cirrhosis and splenomegaly	Performed, non caseating granuloma present	Prednisone (primarily for liver disease)	58	49	448	1.0	52	38	168	1.4	Yes (at diagnosis of hepatic sarcoidosis) Diagnosed by imaging study, liver chemistry test, signs of chronic liver disease and histopathology
4	34	M	Abdominal pain and hepatomegaly on physical exam	Lung and spleen	Hepatomegaly	Performed, non caseating granuloma present	Prednisone (primarily for liver disease)	32	54	188	0.4	20	N.A.	83	0.5	No
5	24	M	None	Lung and eye	Normal	Performed, non caseating granuloma present	Prednisone (primarily for liver and eye disease)	72	124	969	1.9	30	121	82	0.8	No
6	29	F	Abdominal pain and hepatomegaly on physical exam	Lung, joint and cervical lymph node	Hepatomegaly	Performed, non caseating granuloma not present	Prednisone, MTX, SSZ, TNFi and abatacept (primarily for arthritis)	40	85	74	0.9	34	36	93	0.5	No
7	47	F	None	Lung and skin	Normal	Performed, non caseating granuloma present	Prednisone and MTX (primarily for lung and cutaneous disease)	23	27	233	0.5	39	41	96	N.A.	No
8	48	F	None	Lung and eye	Normal	Performed, non caseating granuloma present	Prednisone (primarily for lung and eye disease)	30	25	42	0.5	23	N.A.	N.A.	0.8	No

Case	Age (years)	Sex	Liver signs and symptoms	Other involved organs	Liver imaging at diagnosis*	Liver biopsy	Treatment	At diagnosis				At last follow up				Presence of cirrhosis
								AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (mg/dL)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (mg/dL)	
9	43	F	None	Lung and skin	Normal	Performed, non caseating granuloma present	Prednisone and HCQ (primarily for liver disease)	25	33	399	0.5	26	33	181	0.1	No
10	35	M	None	Lung, spleen and kidney	Low-attenuation nodules	Performed, non caseating granuloma not present	Prednisone (primarily for lung disease)	54	45	361	0.7	54	48	79	0.4	No
11	21	M	None	Lung, eye and parotid gland	Normal	Performed, non caseating granuloma present	Prednisone (primarily for lung and eye disease)	76	158	190	0.7	55	135	110	0.7	No
12	54	M	Abdominal pain	Lung and kidney	Hepatomegaly and low-attenuation nodules	Not performed	None	112	N.A.	1612	0.6	25	15	624	0.4	No
13	45	M	None	Lung	Low-attenuation nodules	Performed, non caseating granuloma present	None	39	N.A.	121	2.3	39	N.A.	137	1.8	No
14	33	F	None	None	Normal	Performed, non caseating granuloma present	None	33	86	157	0.4	23	42	126	0.4	No
15	60	F	Abdominal pain	Lung, spleen and peripheral lymph node	Cirrhosis and low-attenuation nodules	Performed, non caseating granuloma present	None	55	73	240	0.9	34	N.A.	88	1.3	Yes (at diagnosis of hepatic sarcoidosis) Diagnosed by imaging study, liver chemistry test, signs of chronic liver disease and histopathology
16	48	F	None	Lung and eye	Normal	Performed, non caseating granuloma present	None	64	62	506	0.7	49	32	101	0.5	No
17	74	F	Found at autopsy	None	Not performed	Performed, non caseating granuloma present	None	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	No
18	58	M	Found at autopsy	Lung and spleen	Not performed	Performed, non caseating granuloma present	None	61	N.A.	127	N.A.	N.A.	N.A.	N.A.	N.A.	No
19	24	F	Found at autopsy	Spleen and kidney	Not performed	Performed, non caseating granuloma present	None	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	No

N.A., not available; IU, international unit; L, litre; dL, deciliter; mg, milligram; M, male; F, female; MTX, methotrexate; SSZ, sulfasalazine; TNFi, tumor necrosis factor alpha inhibitor; HCQ, hydroxychloroquine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin

Upper normal limit of AST is 43IU/L, ALT 45 IU/L, ALP 118 IU/L and TB 1.0 mg/dL

*Resolution of hepatic nodules with follow-up imaging study were seen in all except one patient (patient no. 15)