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Management of Hepatic Sarcoidosis

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ABSTRACT

Background & Aims: Liver involvement in sarcoidosis may occur in up to 60% of all patients. As many patients experience only minor symptoms, a high number of undiagnosed cases must be assumed. In order to successfully identify patients with hepatic sarcoidosis, a throughout characterization of these patients and their course of disease is necessary.
Methods: We collected 40 patients from four German centers to evaluate current treatment standards and course of disease. All of our patients underwent liver biopsy with histologically proven granulomatous hepatitis.
Results: Detailed characterization of our patients showed an overall benign course of disease. Treatment was very diverse with glucocorticoids for 1 year in 55% (22/40), 5-10 years in 18% (7/40), and permanently in 18% (7/40). Other treatments included disease-modifying anti-rheumatic drugs (DMARDs), the conventional non-biological type in 53% of all patients (of these 81% received azathioprine, 46% metotrexate, 10% hydroxychloroquine, 10% mycophenolate mofetil and 10% cyclophosphamide and biologicals in 8%. Despite these very diverse treatments, patients generally showed slow progression of the disease. Two patients died. None of our patients received a liver transplantation.
Conclusions: Patients received diverse treatments and generally showed slow progression of the disease. Based on our experience, we proposed a diagnostic work up and surveillance strategy as a basis for future, prospective register studies.

Key words: sarcoidosis – liver – hepatic sarcoidosis – diagnosis – treatment.

Abbreviations: ACE: angiotensin converting enzyme; AZA: azathioprine; CT: computed tomography; DMARD: disease-modifying anti-rheumatic drug; HCQ: hydroxychloroquine; LEF: leflunomide; MMF: mycophenolate mofetil; MRI: magnetic resonace imaging; MTX: methotrexate; sIL2R: soluble interleukin 2 receptor; SSZ: sulfasalazine.

INTRODUCTION

Sarcoidosis is a systemic granulomatous disorder of unknown cause, characterized by activation of T-lymphocytes and macrophages. It may affect various organs including the liver [1-4]. The main manifestations are bihilar lymphadenopathy, pulmonary densification, and skin, joint and eye involvement in young adults. Extrapulmonary sarcoidosis occurs in up to 30% of patients, depending on the amount of biopsies, on gender, age at initial diagnosis and ethnicity [5-7]. The mortality of systemic sarcoidosis is 1-5%, mostly due to severe cardiac manifestations [8].

Liver involvement is found in up to 50-65% of patients with extrapulmonary involvement. Of these, only 5-15% are symptomatic. However, as many patients experience only minor symptoms, a high number of undiagnosed cases must be assumed. It is currently believed that hepatic sarcoidosis is often associated with decay of other organs [9-13].

In most patients, diagnosis is made rather late since it usually requires liver biopsy [2]. Histology usually shows well circumscribed non-caseating granulomas. However, the majority of patients with hepatic sarcoidosis are asymptomatic with increased gamma-glutamyl transferase and alkaline phosphatase [14]. Clinically, abdominal pain and itching occur in up to 15% of patients with hepatic sarcoidosis, less often

fever, weight loss, or jaundice. Complications include cirrhosis, cholestatic liver disease with intrahepatic strictures, obstructive jaundice due to portal lymph nodes, portal hypertension, and portal vein thrombosis [14-20].

Angiotensin converting enzyme (ACE) is increased in 75% of the untreated patients [21]. In 20% of the patients, hepatomegaly and ultrasound shows homogeneous liver parenchyma with hypoechoic nodules. Alternatively, abnormalities such as hepatomegaly and multiple hypodense or hypointense masses were described in studies with magnetic resonance imaging (MRI) and computed tomography [8, 12, 13, 22].

The majority of patients with hepatic sarcoidosis does not require any therapy and their courses of disease are often stable or self-limiting. In general, patients with pulmonary, neurological, ophthalmic, myocardial, or renal manifestations require therapy. However, only limited studies are available and reliable treatment recommendations are widely lacking. Currently, treatment is often based on the use of glucocorticoids and other immunosuppressive drugs to prevent granulomatous inflammation and the progression of organ damage.

The currently available evidence on hepatic sarcoidosis was collected decades ago, when treatment of liver disease was clearly different from today's standards. Therefore, we summarized diagnosis, treatment, and course of disease of 40 patients from four German centers in order to evaluate current treatment standards and course of disease.

METHODS

We systematically collected 40 patients from four clinical centers in Germany and analyzed data of the onset and course of the disease as well as laboratory parameters, onset of complications and decompensation, the individual monitoring, and an interpretation of the course due to an individual therapy. Only patients with histologically proven hepatic sarcoidosis were included and analyzed. In detail, criteria for patient inclusion were: 1) biopsy proven granulomatous hepatitis, corresponding non-caseating granulomas of the liver; 2) exclusion of an infectious cause; 3) exclusion of a malignant cause; 4) involvement of at least one additional organ (clinical diagnosis, imaging, or biopsy/histology).

We documented the onset of symptoms and symptoms at diagnosis of the disease, as well as preexisting diseases and concomitant medication, manifestation of sarcoidosis in further organs, histologic examination, laboratory parameters, clinical examination and imaging extracted from the local clinical information systems. Laboratory markers were compared to the course of the disease and changes in therapy. Different medical treatments were also analyzed. Patients were treated at the Department of Internal Medicine II, University Medical Center Mannheim, Germany, the Department of Medicine B, University Medical Center, Münster, Germany, the Department of Internal Medicine I, University Medical Center, Mainz, Germany and the Division of Rheumatology, Nephrology and Haemato-Oncology, Department of Medicine A, Ludwigshafen Medical Center, Ludwigshafen, Germany.

Our retrospective study was approved by the local Ethics Committee II of the University of Heidelberg (Approval No. 2019-871-AF11). All evaluations were performed following the declaration of Helsinki particularly to ensure safety of patients' data. Data was pseudonymized and analyzed before further evaluation.

Statistical analyses included descriptive statistics of the included parameters. Data were analysed with Excel (Microsoft) software.

RESULTS

Symptoms

Seventy-five percent (30/40) of our patients reported symptoms at diagnosis. Pulmonary symptoms were reported by 40% (16/40) of patients, mostly cough and dyspnea. Gastrointestinal symptoms such as nausea or abdominal pain occurred less often in about 8% (3/40). General malaise or deterioration in general condition as well as tiredness/fatigue or B symptoms occurred rarely on its own (Table I). Cardiac manifestations were suspected if patients reported palpations or tachycardia. Some patients reported weakness or difficulty of movement of bones, joints or muscles. Many of these patients reported several symptoms (28%, 11/40). Twenty-seven percent (11/40) of the patients presented with other findings leading to the diagnosis of hepatic sarcoidosis, including elevation of liver enzymes.

Table I. Manifestations reported by patients with hepatic sarcoidosis

Manifestations	Patients n, (%)
No symptoms	9 (22)
Elevation of liver enzymes	11 (27)
Skin disorders	1 (3)
Pruritus	1 (3)
Pulmonary symptoms	16 (40)
Gastrointestinal symptoms	3 (8)
B symptoms - fever/shivering, lymph nodes	5 (11)
Bone/joint pain	3 (8)
Fatigue/weakness	1 (3)
Other	3 (8)

Diagnosis

Laboratory parameters were available at diagnosis and throughout the course of the disease in all 40 patients. However, individual labarotary tests differed considerably among patients and centers. In all patients, in whom soluble interleukin 2 receptor (sIL2R) measurements were available at the time of diagnosis (20/40 patients), all except for one patient had elevated sIL2R levels (average 2,882 U/ml, range of 7 to 12,234 U/ml). ACE was found to be increased in 22/40 (55%, 13 missing) patients with an average 107 U/ml (range 0 to 886 U/ml). In some patients sIL2R and/or ACE were only evaluated after the initiation of glucocorticoid therapy limiting its use as a follow up parameter. 5/40 (13%) patients took an ACE-inhibitor that can influence the laboratory parameter. Vitamin D, C reactive protein (CRP), glomerular filtration rate (GFR), calcium or leukocytes were within a normal range in the majority of patients. Creatinin parameter was not documented in 27/40 patients at the onset of disease. Glomerular filtration

rate was normal in 71 % (15/21) patients (19 missing) at the onset of disease. In isolated cases, no laboratory parameters were available either at initial presentation or during the course of treatment.

Sonography was available for almost all patients and the majority showed initially normal findings (47%, 14/30; 9 missing). However, about 20% (6/30) of the patients showed significant changes in liver ultrasound such as fibrosis or cirrhosis. Seventeen percent (5/30) showed hepatic steatosis and 17% (5/30) had an initial liver mass diagnosed as hepatic manifestation of sarcoidosis (Fig. 1).

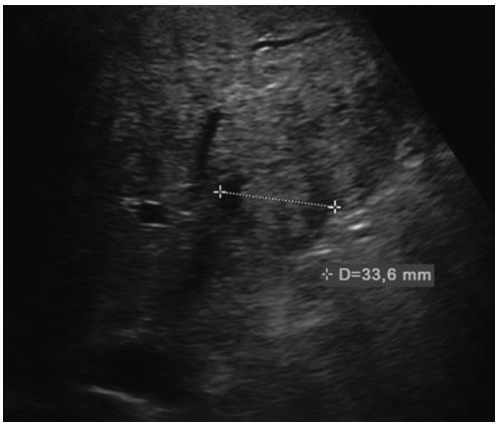

Fig. 1. Mode sonography of the liver displaying a granuloma of 33 mm.

Elastography at diagnosis was available in only 25% (10/40) of all patients. However, this may be partly because many patients had already received the diagnosis of hepatic sarcoidosis more than 10 years ago, when elastography was not broadly introduced into routine diagnosis for hepatic diseases. Of those, 40% (4/10) showed normal values, 20% showed evidence of fibrosis (F1-3) (2/10) and 40% showed evidence of cirrhosis (4/10). In 45% (18/40; 22 missing) of patients follow up with ultrasound was available. We observed no changes in the course of disease in 61% (11/18; 22 missing), a follow-up elastography was available in 18% (7/40) of our patients. Monitoring elastography parameters revealed that 14% (1/7) of patients experienced worsening of their fibrosis compared to the first available examination. Imaging procedures such as MRI or CT examination as an additional examination were only applied for clarification of specific questions, e.g. in the case of an unclear mass of the liver in a few patients.

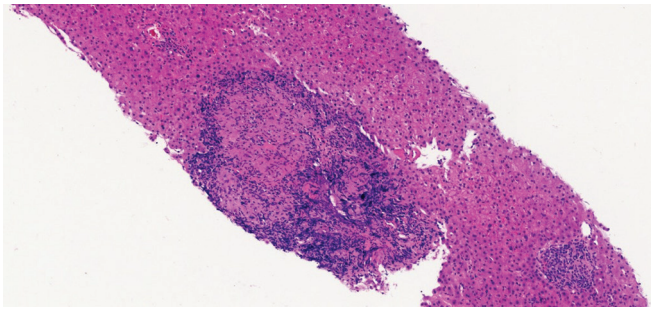

Fig. 2. Hepatic granuloma in an hematoxylin & eosin (H&E) stained liver biopsy.

An esophagogastroduodenoscopy was performed initially or during the course of the disease in 53% (21/40) of patients. No evidence of esophageal varices was reported in 90% (19/21) of patients; high-grade esophageal varices (grade III) requiring intervention were found in 10% (2/21) of these patients.

All patients received a liver biopsy.

Extrahepatic Manifestations of Sarcoidosis

At least one extrahepatic biopsy was also performed in 60% (24/40) of the patients, mostly pulmonary, lymph nodes and kidneys. 54% (13/24) received biopsies of the kidneys.

In 68% (27/40) of the patients with hepatic sarcoidosis, a co-occurring pulmonary manifestation was also confirmed histologically or suspected by clinical parameters, laboratory findings or imaging characteristics. Lymph nodes were affected histologically proven in 35% (14/40) and suspected in additional 3 patients. Kidneys' involvement were histologically proven in 25% (10/40) and suspected in additional 3 patients. Skin changes as a clinical manifestation or histologically proven were found in only 10% (4/40) of the patients. Joints were affected in 13% (5/40). Besides, skeletal manifestations existed in about 10% (4/40). Neurological evidence was only found in 3% (1/40). There were no proven muscular involvements but we had 15% (6/40) clinically suspected cases. Splenic manifestation was histologically confirmed in 3% (1/40) and suspected in additional 5% (2/40) of patients due to splenomegaly. Ocular involvement such as blurred vision but also asymptomatic manifestation occurred in as many as 10% (4/40) of the patients. Cardiological involvement was proven histologically in only 3% (1/40) of the patients, but 10% (4/40) of the patients showed clinical evidence of cardiological involvement, e.g. palpitations.

Preexisting Medical Conditions

Most patients (80%, 32/40) presented with pre-existing illness, particularly cardiovascular diseases, e.g. cardiac insufficiency and coronary heart disease. Furthermore, 18% (7/40) of patients presented with thyroid disease and diabetes mellitus. About 10% (4/40) of the patients were obese. Only 20% (8/40) of our patients did not report any pre-existing or additional disorders.

Preexisting Medication

The majority of patients were initially taking medication for other diseases. Particularly cardiovascular medication such as ramipril was taken by 43% (17/40) as well as acetylsalicylic acid in 10% (4/40). Vitamin D consumption was also common. Ten percent of patients (4/40) were prescribed ursodesoxycholic acid. Thirteen percent of patients (5/40) did not take any medication.

Therapy

Treatment of these patients (Table II) was mainly based on glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs): the conventional (csDMARD) and biological type (bDMARD). Most patients (90%, 36/40) received glucocorticoid therapy for sarcoidosis with hepatic manifestation. Treatment of these patients was very diverse with glucocorticoids for 1 year in 55% (22/40), 5-10 years in 18% (7/40), and permanently

Table II. Therapeutic options in hepatic sarcoidosis

Therapeutic agent	Dosage	Indication	Side effects	Hepatotoxicity
Glucocorticoids	1 mg/kg/d, individual tapering schedule	Sarcoidosis systemic or organ specific; initiation of treatment, longterm in combination with further immunosuppressive drugs	Cushingoid features, weight gain, osteoporosis, hyperglycemia, hypertension, glaucoma, depression, sleep disturbance	possible
Azathioprine	50 – 150 mg /d	Corticoid-sparing, hepatic manifestation	Pancreatitis, hepatitis, oral ulcers, myalgia, malaise, infections, malignacy	possible
Leflunomide	20 mg /d	Corticoid-sparing, pulmonary + ocular manifestation	Alopecia, diarrhea, nausea, elevation in liver enzymes, rash, hypertension	yes
Metothrexate	s.c. 15 mg 1x/week	Corticoid-sparing, hepatic manifestation		yes
Hydroxychloroquine	200-400 mg/d, max. 5mg/kg	Dermatologic + joint manifestation	Macular toxicity	yes
Mycophenolate mofetil	2x500-1000 mg/d	Corticoid-sparing, hepatic manifestation	Diarrhea, leucopenia, infections, malignancy	possible
Infliximab	i.v. 3,5 mg/kg		Gastrointestinal side effects, headache, infections, anaphylactic reactions	possible
Adalimumab	s.c. 40 mg every 2 weeks		Gastrointestinal side effects, headache, infections, anaphylactic reactions	possible

in 18% (7/40) of patients. Detailed information on other treatments was available in 21 patients. Applied drugs included csDMARDs in 53 % (21/40). Of these 81% (17/21) patients had received azathioprine (AZA), 46% (10/21) methotrexate (MTX), 10% (2/21) hydroxychloroquine (HCQ), furthermore 10% (2/21) mycophenolate mofetil (MMF), and 10% (2/21) cyclophosphamide. Biological DMARDs were administered to 8% (3/40) of all patients. There was no significant association between patients who had an increased sIL2R or ACE initially or during the course and patients who received DMARDs.

Concerning analysis of correlation, the use of HCQ was not associated with any changes in follow-up sonography. Concerning MMF, cyclophosphamid or biologicals no associations were reported.

Course of Disease

Observation time differed among patients; the shortest period was 4 months; the longest period was 13 years.

Two patients died within the observation time. One suffered from a septic shock and subsequent liver failure due to a spontaneous bacterial peritonitis and acute liver and kidney failure due to hepatorenal syndrome. The other one died from progressive liver failure.

However, the majority of patients 54% (18/33) did not suffer from life threatening progress of hepatic sarcoidosis within the observation time. 42% of patients (14/33) progressed with development of a fibrosis or cirrhosis. In 6% (2/33) subsequent complications of liver cirrhosis were observed. None of our patients received a liver transplantation. In 6 patients follow up was not available.

DISCUSSION

The lack of knowledge about the etiology, course of the disease, complications, and outcome of liver sarcoidosis makes the evaluation of prognosis and individual course of disease difficult. Better characterization and structured assessment of patients in clinical registries would certainly improve understanding of the disease. However, given the rareness of the disease, lack of current data on the course of disease, but also heterogeneity in diagnostic and treatment approaches to hepatic sarcoidosis, it seems necessary to first compile and characterize a number of these patients and define the current view on hepatic sarcoidosis in hepatologic expert centers.

Liver involvement in sarcoidosis is common, but only 5-15% of patients show liver disease-related symptoms [21]. A considerable number of patients were asymptomatic, and disease was solely detected on the basis of elevated liver enzymes or abnormal imaging studies, comparable to the autopsy studies. In a recent US population-based study, 63% (12/19) of patients with hepatic involvement of sarcoidosis were asymptomatic [23]. However, earlier post-mortem studies from autopsies of patients with confirmed sarcoidosis had demonstrated that up to 70 % of patients also suffered from a hepatic manifestation [24-26]. In contrast to the above mentioned reports, most of our patients did report symptoms leading to the diagnostic procedures of the disease; (28%, 11/40) of them even reported multiple symptoms, particularly pulmonary symptoms.

Simultaneous sarcoidosis in other organs was also histologically confirmed or clinically suspected in most of our patients, especially in the lungs (70%), lymph nodes (38%), and kidneys (42%). In a previous multicenter study, intrathoracic lymph nodes (77%), pulmonary involvement (73.5%), skin involvement (16.1%) were the most commonly involved organs of systemic sarcoidosis, whereas renal involvement was only 3.3% [27]. Besides, skin changes, joints and osseous manifestation, neurological, spleen and ocular involvement were found in less than 10% of our cases, as also reported in other studies [28-33], further emphasizing the systemic nature of the disease. Cardiological manifestation was proven histologically in only 3% (1/40) of the patients whereas approximately 10% (4/40) showed clinical evidence of cardiological involvement. This is also an important issue as sarcoidosis patients manifesting with cardiac involvement usually show worse prognosis than those without cardiac

involvement [34]. Yazaki et al. [35] reported that the five-year overall survival of 95 Japanese patients with cardiac sarcoidosis was 60%, same as the overall transplantation-free five-year survival rate in another multicenter study [36].

Diagnosis differed considerably between centers in our study. Laboratory abnormality is usually the first step to identify patients. ACE was increased in 81% of patients (13 missing) and therefore higher compared to the previously reported 65.5% of 39 patients reported by Fetzer et al. [37]. But the role of ACE in the diagnosis of sarcoidosis is still uncertain, as it was reported to be non-specific and not sensitive enough [23, 38, 39]. Furthermore, therapy with ACE-inhibitors can confound ACE-levels. Meanwhile, sIL2R, a marker of T-cell activation which correlates with disease activity in many diseases including sarcoidosis, was proposed to have a better specificity and sensitivity than ACE [40, 41]. It is to be mentioned that sIL2R is not specific for granulomatous hepatitis and can be increased after transplantation or rejection of transplanted organs, in lymphoma, solid tumors and many more. In our cohort, sIL2R was tested initially and elevated in all besides one patient. Although it is unclear as to why sIL2R was not tested in all patients, this certainly reflects a lack of awareness and knowledge but also a lack of standards on the treatment of hepatic sarcoidosis.

Sonography was performed on almost all our patients, and most patients showed normal findings. Elastography was not broadly used in our cohort, and MRI or CT examination was also only applied as additional examination in specific situations. This may be due to a considerable number of patients being diagnosed before 2003 where elastography was not implemented in routine hepatology work up procedures.

However, all our patients received a liver biopsy (as selection of our patients was based on liver histology), and all of them revealed non-caseating granulomas. Particularly in patients with lack of other organ involvement, a biopsy seems to be important in order to exclude viral, metabolic or autoimmune liver disease. Furthermore, differential diagnosis of granulomas includes neoplasia (lymphoma of Hodgkin), infectious entities (e.g. tuberculosis, Q-fever, brucellosis, mycotic infection), drug-associated and idiopathic changes as well as autoimmune phenomena such as primary biliary cholangitis [42-45]. However, as a biopsy was performed in most patients with suspected sarcoidosis before treatment in all centers, the necessity of a histological confirmation can be assumed to be generally accepted.

Treatment of our patients was very diverse with glucocorticoids for 1 year in 55%, 5-10 years in 18%, and permanently in 18% of patients. Other treatments included DMARDs with cDMARDs in 53% of patients and bDMARDs in 8%. Targeted DMARDs were not applied. Initial therapy was usually performed with glucocorticoids which are thought to be effective [46]. A British 180-patient study by Kennedy et al. [47] showed a complete response to treatment in one-third of the patients and no response or partial response in one-third of patients each. However, the optimal or adequate duration of glucocorticoids treatment remains unclear. Despite the hepatotoxicity of MTX, treatment may be considered and effective in cases not responding to initial therapy [48, 49]. Ten of our 40 patients (46%) received MTX. Five patients with intrahepatic cholestasis, jaundice and pruritus received ursodeoxycholic acid (UDCA). However, since it was mostly administered in combination with other (immunosuppressive) drugs, the effect of UDCA itself remains unclear.

Prognosis of the individual course of the disease in patients with hepatic or multi-organic sarcoidosis is difficult. Mortality of systemic sarcoidosis is about 1-5% often due to severe cardiac manifestation [50]. Judson et al. and Baughman et al. published several studies about sarcoidosis with or without hepatic manifestation [51-60]. In summary, the individual courses of hepatic manifestation seemed difficult to compare. Often patients show mild, oligosymptomatic courses, although fast progression with complications, liver insufficiency, and failure with the need for transplantation is possible. In our cohort only two patients died within the observation time ultimately due to spontaneous bacterial peritonitis and liver failure. However, we did not observe one single fast progressing disease manifestation in our patients.

In our study, treatment with either glucocorticoids or immunosuppressive agents and also very diverse treatment regimens did not show any difference in outcome. Although patients with hepatic manifestation of sarcoidosis were followed for many years, in the majority of patients the disease was stable or only slowly progressing. Thus, the effect of (immune suppressive) treatment remains unclear. None of our patients received liver transplantation within the period of observation. Thus, none of our patients met a clearly measurable endpoint that would allow to discriminate between effective and ineffective treatment. This is also in line with previous data. Although none of our patients underwent liver transplantation, as curative therapeutic intervention, liver transplantation is possible for patients with a complex or life-threatening course [19, 61-68]. According to a study by Vanatte et al. [61] from the United States, among 87,392 liver transplantations listed in the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) database, only a very small group of 43 patients was transplanted for hepatic sarcoidosis, and these recipients with hepatic sarcoidosis reported survival rates of 78% and 60% at one and five years, respectively. Relapse in the transplanted liver is still possible [69], but the probability is low. Even lower was the probability of complications such as transplant insufficiency and death.

Given the generally slow progress of hepatic sarcoidosis, no evidence has been published on structured follow-up and surveillance of patients with hepatic sarcoidosis [39, 70, 71]. Experts' recommendations are usually based on pulmonary sarcoidosis with hepatic manifestation.

Based on our study, we propose the following structured monitoring for patients with hepatic sarcoidosis acknowledging the current lack of structured data collection in these patients: 1) Basic diagnostics at confirmation of hepatic sarcoidosis: extensive medical history including fatigue, weight loss, fever, substance abuse etc., liver enzymes and synthesis parameters (albumin, prothrombin time), serological evaluation for viral hepatitis (hepatitis A, B, C, E), metabolic diseases, glucose, HbA1c, ferritin, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin test (A1AT) and autoantibodies ANA, AMA, SMA, LKM, SLA. 2) Sonography and elastography are essential parts

Table III. Proposed diagnostic pathway of hepatic sarcoidosis.

	First visit	After 2-3 weeks	Every 3 months	Every 6 months	Every 12 months
Active disease or Start of treatment	MH, PE, Lab-i, SE, ECG, CR, LT, OE, biopsy	MH, PE, Lab-m1	MH, PE, Lab-m1	MH, PE, Lab-m6, SE	MH, PE, Lab-m12, SE, ECG, CR, LT, OE
Inactive disease	MH, PE, Lab-i, SE, ECG, CR, LT, OE, biopsy	X	X	X	MH, PE, Lab-m12, SE, ECG, CR, LT, OE

Special examination based on symptoms: high resolution CT scan, echocardiogram, Holter monitoring, urine analysis, TSH, bone density, cMR; MH: medical history i.e. malaise, fever, weight loss, fatigue, dyspnea, cough, abdominal pain, palpitation, syncope, sight disorder; PE: physical examination i.e. lung, heart, abdomen, skin, lymph nodes; Lab: laboratory parameters: Lab-i: initial laboratory parameters i.e. complete blood count, creatinine, calcium, AST, ALT, alkaline phosphatase, bilirubin, albumin, INR, ACE, sIl2R, 25-OH-vitamin D, Lab-m1, Lab-m6, Lab-m1 : see Lab-i. SE: sonography and elastography; OE: ophthalmologic examination; CR: chest X-ray; LT: lung tests (spirometry, diffusing capacity, 6 minute walking test); HRCT: high resolution CT scan

of an initial status. 3) liver biopsy is needed to confirm hepatic sarcoidosis. 4) Chest X-ray as well as a physical examination of skin, lungs, and lymph nodes are crucial to detect additional organ manifestations of the disease. 5) Furthermore, serological testing needs to be extended to include kidney function, blood count, calcium and vitamin D. 6) Furthermore, we recommend an ECG for the first visit and further examination based on symptoms (e.g. high resolution CT scan, echocardiogram etc.). Clinical practice guidelines for sarcoidosis recommends an ECG, echocardiogram and 24h – ECG. 7) If symptoms suspicious for eye involvement occur, we recommend an eye examination (Table III).

We do not recommend biopsies of all organs with possible involvement at the onset of the disease, but we recommend a biopsy of organs with either clinical or laboratory abnormalities.

In our experience follow up every three months with physical exam, and serologic evaluation particularly liver enzymes, cholestasis parameters and synthesis seemed well suited for these patients. An ultrasound every 6 months seemed safe given the slow progression documented in our patients.

These intervals should be reduced to four weeks in the case of treatment initiation or changes in treatment.

CONCLUSIONS

Diagnosis of hepatic sarcoidosis remains challenging, and approaches vary widely even among hepatological expert centers. Treatment of these patients was very diverse with glucocorticoids in most patients but also DMARDs (conventional and biological) in some patients. Despite these very diverse treatments, patients generally showed only slow progression of the disease. Throughout the observation time only two patients died due to spontaneous bacterial peritonitis and liver failure. None of our patients received a liver transplantation.

Based on our experience, we proposed a detailed diagnostic work up and surveillance strategy as a basis for future, prospective register studies.

Conflicts of interest: None to declare.

Authors' contribution: J.S., R.B., A.T. designed the study. J.S., B.S., M.W., C.A., C.A.W., R.B. collected the data.J.S., B.S., H.J.S., M.W., P.R.G., Y.Q., S.H., R.B., M.P.E., A.T. analysed the data. J.S., B.S., H.J.S., M.W., P.R.G., Y.Q., C.A., C.A.A., S.H., R.B., M.P.E., A.T. drafted the manuscript. H.J.S., P.R.G., M.P.E. critically revised the manuscript for intellectual content. All the authors read and approved the final version of the manuscript.

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