Rare disease

Diagnostic and therapeutic challenges of hepatic sarcoidosis

Haider Mosea,¹ James Gotto,² Zubair Khan²¹Gastroenterology Department, Cheltenham General Hospital, Cheltenham, Gloucestershire, UK;²Gastroenterology Department, Yeovil Foundation Hospital, Yeovil, Somerset, UK**Correspondence to** Dr Haider Mosea, Dr.H.Mosea@doctors.org.uk**Summary**

The authors report three cases of hepatic sarcoidosis complicated by portal hypertension in Caucasian patients. The cases varied in their presentations from normal liver function to symptomatic cholestasis and established liver cirrhosis. In one particular case the authors discovered hepatic sarcoid after a diagnostic gastroscopy for upper gastrointestinal (GI) bleeding which showed changes of portal hypertension. In all of these cases the authors gave our patients a prolonged course of immunosuppressive treatment with over all good long-term results. The authors hope that our work will provide a modern approach into treating this disease.

BACKGROUND

Hepatic sarcoid disease is a rare condition and clinical debate remains widely open regarding efficacy of long-term immunosuppression.

CASE PRESENTATION

The first case is a 40-year-old woman presenting with symptomatic cholestasis and feeling generally tired most of the time, she was found to have mild hepatosplenomegaly.

She had an established diagnosis of pulmonary sarcoidosis with history of granulomatous uveitis and unilateral

facial palsy. Immunosuppression in this case with 40 mg prednisolone, resulted in good symptomatic and biochemical improvement. Interestingly, there was an evident chemical and clinical relapse every time the steroid dose was reduced.

The second case was a 75-year-old man presenting with hypercalcaemia and urolithiasis, he then developed an acute upper GI bleeding, marked hepatosplenomegaly, while his liver function tests (LFTs) remained normal all the way through.

His endoscopy showed, much to our surprise, changes of severe portal hypertension and oesophageal varices. To

Figure 1 2002 Biopsy showing non-caseating granulomatous inflammation within portal tracts highlighting the connective tissue/fibrosis (Masson trichrome) around the granulomata (blue), granulomata in middle, sheets of hepatocytes either side.

Figure 2 2007 Biopsy showing connective tissue stain (Masson trichrome) with less portal fibrosis than previous biopsy and no granulomata in portal tracts.

our amazement, those changes of gastropathy were later confirmed on endoscopy to have responded well to treatment with azathioprine. The improvement was also seen for the first time on histological basis as we had arranged for an interval liver biopsy for this purpose. While the previous liver biopsy, that confirmed the diagnosis in this case, showed extensive cirrhotic changes (see figure 1), the repeat liver biopsy showed a more organised reaction, (see figure 2).

Our last case is most unusual for a 71-year-old man presenting with isolated hepatic sarcoid and symptomatic cholestasis plus marked splenomegaly but without hepatomegaly. He had a previously established diagnosis of cardiac sarcoidosis, presenting with conduction disvaease requiring a permanent cardiac pace maker. Immunosuppression in this case resulted in good symptomatic and biochemical improvement, but unfortunately led to a difficulty in eradicating the *Mycobacterium* infection in a prosthetic hip joint.

INVESTIGATIONS

All our three patients had a serum ACE level checked with an ultrasound scan of the abdomen and/or CT scan of the liver done as standard tests. In all cases, autoantibodies, hepatitis serology and routine liver screen tests were negative. Diagnostic liver biopsies were performed in all three cases, as well as diagnostic gastroscopy.

In case 1, patient had an elevated serum ACE at 86 nml/ml/min. A CT scan of the chest demonstrated mediastinal lymphadenopathy. Therefore she was referred for mediastinoscopy and lymph node biopsy which confirmed the diagnosis of sarcoidosis. An ultrasound of the liver showed

mild splenomegaly, moderate hepatomegaly with a diffuse hepatic echo texture. She proceeded to have a diagnostic liver biopsy which showed granulomatous hepatitis consistent with liver sarcoid.

A diagnostic gastroscopy was then arranged in order to look for endoscopic changes of raised portal pressure, this only showed mild changes of portal hypertensive gastropathy with no varices.

In case 2, patient's blood test results also demonstrated an elevated serum ACE at 85 nml/ml/min. A CT scan of the abdomen showed moderate hepatosplenomegaly, enlarged portal vein and prominent hepatic venules and para-aortic lymph nodes. A diagnostic liver biopsy showed non-caseating granulomatous hepatitis with moderate irregular fibrosis, see figure 1.

A repeat liver biopsy few years later showed remarkable improvement, see figure 2. An urgent therapeutic gastroscopy was indicated in this case as it presented with an acute upper GI bleed; it showed an actively bleeding gastric ulcer, one oesophageal varix and changes of severe portal hypertensive gastropathy for which later argon plasma coagulation treatment was applied.

Patient then had a follow-up repeat gastroscopy showing significant endoscopic response to treatment.

The patient in case 3 had the highest level of serum ACE in this series, being elevated at 113 nml/ml/min. An ultrasound of the abdomen demonstrated marked splenomegaly, normal liver and gall stones with no obstruction of the common bile duct which was confirmed on CT cholangiogram. A diagnostic liver biopsy showed non-caseating granulomas, while an elective diagnostic gastroscopy showed only mild portal gastropathy.

DIFFERENTIAL DIAGNOSIS

This essentially includes any cause for deranged LFT!

(A) Infectious diseases	
Actinomycosis	Lyme disease
Listeriosis	<i>Staphylococcus</i> infections
Syphilis	TB
<i>Mycobacterium avium</i> intracellulare	Leprosy
BSG immunisation	Q Fever
Psittacosis	Aspergillosis
Candidiasis	Histoplasmosis
CMV	EBV
Hepatitis A	Varicella
Amoebiasis	Giardiasis
Schistosomiasis	Toxocariasis
(B) Drugs	
Allopurinol	Nitrofurantoin
Phenytoin aspirin	Sulfonamides
Carbamazepine isoniazid	Diltiazem
Quinidine	Penicillin
Chlorpromazine	Tolbutamide
(C) Metals, for example, copper and gold	
(D) Immunological diseases	
Hypogammaglobulinaemia	Polymyalgia rheumatica
Primary biliary cirrhosis	Rheumatic fever
SLE	Polyarteritis nodosa
Temporal arteritis	Wegener's granulomatosis
(E) Neoplasms	
Hodgkin disease	NHL
Hepatocellular adenoma	Extrahepatic malignancy
(F) Miscellaneous	
IBD	Whipple's disease
Porphyria cutanea tarda	Psoriasis
Sickle cell anaemia	Sarcoidosis

CMV, cytomegalovirus; EBV, Epstein-Barr virus; IBD, inflammatory bowel disease; NHL, non-Hodgkin lymphoma; SLE, systemic lupus erythematosus; TB, tuberculosis.

TREATMENT

In all three cases, a standard dose of 40 mg prednisolone was commenced at the very start of the treatment course.

This was followed by introducing azathioprine, achieving remarkable clinical, biochemical as well as endoscopic and histological improvement as evident in case 2.

The length of the treatment course was mainly decided by our patient's response, there was an evident clinical and biochemical relapse whenever immunosuppressants dosage was reduced especially in case 1.

Our patients have essentially tolerated their treatments very well; one exception is case 3, where our patient developed a severe mycobacterial infection requiring 2-year treatment with antituberculosis(anti-TB) medications.

OUTCOME AND FOLLOW-UP

The patient in case 1 achieved good symptomatic improvement and managed to get rid of her disabling tiredness, her LFT results have also improved but they have never gone back to normal.

In this particular case, reducing prednisolone to less than 10 mg resulted in severe tiredness and deterioration in liver function, the possibility of Addison's disease was obviously looked at and clinically excluded.

In case 2, we also noted significant improvement of patient's symptoms, degree of gastropathy and liver cirrhosis, patient was kept on azathioprine for a few years.

Five years later, a repeat liver biopsy in this case showed only mild inflammation, with bridging fibrosis, no cirrhosis or granulomas were seen (figure 2).

Our patient in case 3 had his azathioprine switched to mycophenolate leading to symptomatic and biochemical improvement, he however, was later admitted with back pain. A lumbosacral CT scan showed spinal cord compression at T10-T11 and moderately large gluteal mass, extending to a prosthetic right hip joint.

Examination of aspirated fluid revealed *Mycobacterium avium* intracellulare (MAI). A repeat CT scan 2 years later showed significant improvement, however, repeat fluid aspirate still shows presence of MAI despite 2 years of quadruple anti-TB treatment and stopping immunosuppressant therapy.

DISCUSSION

Only a few cases have been published about isolated liver sarcoidosis, one similar case in which TB occurred as a complication, no previous publication in which an interval liver biopsy was used as a monitoring tool.

Aetiology of sarcoidosis remains yet to be discovered, it has a characteristic immunopathogenesis that involves reduction of the number of circulating helper T lymphocytes as they cluster themselves in different body organs, persistently proliferating, leading to a chronic granulomatous inflammation.

These are non-caseating granulomas which upon forming too many clumps in an organ start to interfere with that organ's function, they also send chemotactic signals to recruit macrophages to the involved tissues causing depressed peripheral cellular immunity (anergy) and stimulation of humoral immunity with hypergammaglobulinaemia.^{1 15}

The prevalence of systemic sarcoidosis is 1-40/100 000, being predominantly observed in African-Americans and in persons of Scandinavian descent, affecting mostly young adults between 20 and 40 years of age.¹³

Sarcoidosis can affect any body organ. It most commonly affects the lungs (90%), lymph nodes (75%), eyes (25%) and skin (25%).²² Sixty-six per cent of systemic sarcoid patients will have some form or another of associated liver involvement,⁵ but isolated liver sarcoid is extremely rare.

The spectrum of hepatic sarcoidosis ranges from, clinically silent granulomas in an asymptomatic patient which is the most common, to incidental deranged LFT, hepatosplenomegaly and adenopathy incidentally found on CT abdomen followed in frequency by focal low attenuation lesions of the liver and spleen, fever (pyrexia of unknown origin), jaundice and chronic cholestasis, pruritus, nausea and vomiting, right upper quadrant pain, extrahepatic biliary tract obstruction from enlarged granulomatous lymph nodes, Budd-Chiari syndrome, intrahepatic cholestasis resembling primary biliary cirrhosis or sclerosing cholangitis and portal hypertension from granulomas in the portal triad, usually with relatively preserved liver function.

Ascites may also occur, which is usually a transudate from right heart failure (because of pulmonary hypertension) or portal hypertension (because of biliary cirrhosis). Rarely, an exudative ascites may occur from studding of the peritoneum with nodules. Pancreatic involvement

presents as a mass, usually in the head or a diffusely firm, nodular organ.

ACE, is increased in 55% of patients with sarcoidosis, with a higher frequency in those with active disease.¹¹

Therefore liver biopsies remain a valuable tool for diagnosis and also for disease monitoring in patients with liver sarcoidosis.

Overall, treatment for hepatic sarcoidosis is targeted toward alleviation of symptoms but has no curative potential at this time.⁸

Immunosuppression is recommended for the minority of patients who progress to chronic cholestatic disease, portal hypertension and cirrhosis. Treatment of hepatic sarcoidosis should be reserved for those patients who manifest this spectrum of disease as early steroid treatment does not preclude the development of intrahepatic cholestasis or development of portal hypertension.

Glucocorticoid treatment is first-line therapy for hepatic sarcoidosis, improving symptoms and abnormal laboratory values but generally having no effect on progression of disease. In addition to glucocorticoids, immunomodulators such as azathioprine, methotrexate, hydroxychloroquine and infliximab have been used with some positive effects on symptoms, liver enzyme abnormalities and hepatomegaly, but again none has been shown to preclude the development of portal hypertension.

In our reported case 2, however, we have shown significant histological improvement on repeat liver biopsy following 5 years of continuous immunosuppression which also led to improvement in portal hypertension changes as proven on repeat endoscopies in a patient with severe portal hypertension and cirrhosis due to liver sarcoidosis.

Ultimately, in cases of severe portal hypertension and cirrhosis with overt liver failure, seen in only 1% of cases, then liver transplantation is the definitive treatment. Interestingly, recurrence of disease in the allograft has been reported in a previous case.¹²

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Competing interests None.

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Learning points

- ▶ M1 – sarcoidosis is a systemic inflammation
- ▶ M2 – exclusive hepatic sarcoidosis is rare
- ▶ M3 – portal hypertension may develop in the absence of true cirrhosis
- ▶ M4 – sarcoid granulomas in the liver are small and preferably located
- ▶ M5 – clinical hepatic manifestations are rare
- ▶ M6 – diagnosis requires high index of suspicion
- ▶ M7 – immunomodulators have some positive effects on symptoms, liver enzyme abnormalities and hepatomegaly, but debatable effect on progression of disease.

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