CASE REPORT

Hepatic Sarcoidosis: Diagnostic approach and management

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SUMMARY

Sarcoidosis is a multi-systemic, non-caseating granulomatous disorder with an idiopathic aetiology. We report a 58-year-old Malay woman, with underlying type II diabetes mellitus, hypertension and history of stage II pulmonary sarcoidosis presenting with incidental finding of multiple hypodense liver lesions. Her recent contrasted enhanced computed tomography of the abdomen and pelvis demonstrated multiple intra-abdominal lymphadenopathies with evidence of liver and splenic infiltrations. Her age-appropriate malignancy screening was negative while liver biopsy showed non-caseating granulomatous hepatitis consistent with hepatic sarcoidosis. In view of her normal liver enzymes and normalised serum calcium levels, no immunosuppressive therapy was commenced. She remains asymptomatic and is currently under our close monitoring.

INTRODUCTION

Sarcoidosis is a multi-systemic, non-caseating granulomatous disorder. It remains an enigma due to its idiopathic aetiology, wide-ranged presentations and unpredictable prognosis. Sarcoidosis is more prevalent among female compared to male, with an incidence of 6.3 and 5.9 cases per 100,000 populations respectively.[1] The lifetime risk for Caucasians in the United States of America is estimated at 0.85 percent.[1] However, sarcoidosis is less common among Asian communities. The estimated annual incidence of sarcoidosis in Singapore was 0.56 per 100,000.[1] Currently, there is no up-to-date information of sarcoidosis in Malaysia and literature search showed around 10 reported cases from year 2000 till 2021 (Table I). The onset of sarcoidosis can be insidious, and abnormalities may be discovered only on routine chest radiograph while skin involvement is seen in 25% of patients and may be the only site of involvement.[1] Hence, clinical suspicion is vital in reaching the diagnosis.

CASE REPORT

A 58-year-old Malay woman, with underlying type II diabetes mellitus and hypertension for 10 years was initially referred from the local community clinic three years ago for bilateral hilar lymphadenopathy from a screening chest radiograph done for chronic cough. Her contrasted enhanced computed tomography (CECT) thorax demonstrated bilateral hilar and mediastinal lymphadenopathies. Endoscopic ultrasound (EUS) guided biopsy of her mediastinal lymph nodes revealed multiple non-caseating granulomatous lesions and she had a negative mycobacterium tuberculosis work-up. She was diagnosed with stage II pulmonary sarcoidosis with disturbing respiratory symptoms and deteriorating lung function results (FVC and DLCO) on her serial follow-up. She was prescribed with oral prednisolone 0.5mg/kg per day for four weeks and taper upon improvement of her symptoms and lung function test. She achieved successful resolution of her bilateral hilar lymphadenopathy and her lung function test improved back to normal over one year duration. Unfortunately, she missed her appointments subsequently due to resolved symptoms.

One year later, she was referred by her primary care doctor for asymptomatic hypercalcemia (Table II). There were fine crepitations on her bilateral lung fields with hepatosplenomegaly on clinical examination. There was no palpable lymphadenopathy. Otherwise, there was absence of erythema nodosum, arthritis and parotid swelling. A repeated CECT thorax (Figure 1) showed mediastinal and intra-abdominal lymphadenopathy with infiltrations into her liver, spleen, and lung parenchyma. There was no evidence of portal hypertension. She remained asymptomatic. Her six minutes walking test yielded a good total walking distance of 228 metres without desaturation. Her latest lung function test showed a severe restrictive pattern with FEV_1 of 49% and FEV_1/FVC of 0.9. In view of hypercalcemia and raised alkaline phosphatase, an extrapulmonary sarcoidosis workup was commenced. Her serum Angiotensin Converting Enzyme was raised at 172U/L. A CECT abdomen and pelvis (Figure 1) demonstrated multiple intra-abdominal lymphadenopathies with evidence of liver and spleen infiltrations. A liver biopsy was performed to rule out malignancy or tuberculosis. Histopathological examination of her liver biopsy (Figure 2) showed non-caseating granulomatous hepatitis consistent with hepatic sarcoidosis in view of her past history of pulmonary sarcoidosis. Both Ziehl-Neelson stains for acid-fast bacilli and Periodic Acid-Schiff (PAS) indicate glycogenation for presence of fungi were negative. Liver biopsy for tuberculous polymerase chain reaction (PCR) and *Mycobacterium tuberculosis* culture were negative. Her age-appropriate malignancy screening, human immunodeficiency virus and autoimmune workup were all negative. Echocardiography showed a normal left ventricular ejection fraction of 60% with no evidence of pulmonary hypertension. Her attending hepatologist decided to monitor her first as she was asymptomatic. She had no evidence of nephrocalcinosis, nephrolithiasis, ocular, neurologic and myocardial sarcoidosis involvement.

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Table I: Sarcoidosis case reports in Malaysia from year 2000-2021

No.	Study, year	Age/sex	Site of sarcoidosis	Management
1.	Wan Muhaizan WM, 2004[2]	26/male, 47/male	Pulmonary, cardiac	Nil
2.	Ismail S et al., 2005[3]	40/male	ocular	Oral and topical steroids
3.	Ramlee N et al., 2007[4]	42/female	conjunctiva	Oral steroids and surgery
4.	Ling PK, 2009[5]	43/male	Abducens nerve, cervical lymphadenopathy, cardiac	Steroids
5.	Ahmad Y et al., 2010[6]	29/male	Pulmonary, liver, parotids, lymphadenopathy	Steroids
6.	Sazliyana Shaharir S et al., 2017[7]	59/male	Proximal myopathy, lymphadenopathy	Steroids and azathioprine
7.	Chang A et al.,2018[8]	27/male	Pulmonary	Observation
8.	Noorhafini AS et al., 2020[9]	43/female	Pulmonary, liver , facial nerve	Steroids and azathioprine
9.	Tan WJ et al., 2021[5]	38/female	Pulmonary , myocardium	Steroids
10.	Low QJ et al, 2021[10]	30/female	Pulmonary	Steroids

Table II: Laboratory investigations

Blood parameters	Reference range	Pulmonary sarcoidosis diagnosis at 2017	Hepatic sarcoidosis diagnosis at 2020	On discharge
Haemoglobin	12-18g/dL	13	13.1	14
Platelets	150 x 10^3- 450x10^3/microlitre	200	350	300
White Cell Counts	4 x 10^3- 9x10^3/microlitre	7	6.44	5
Sodium	135-145mmol/L	132	133	134
Potassium	3.5-5.1mmol/L	4	4.4	3.9
Urea	2.8-7.2mmol/L	3.9	8.5	5.8
Creatinine	59-104micromol/L	52	157	128
Corrected calcium	2.2-2.65mmol/L	2.66	3.03	2.40
Total protein	66-83g/L	80	89	92
Albumin	35-52g/L	31	33	35
Globulin	28-36g/L	45	55	57
Total Bilirubin	5-21micromol/L	10	12.9	11.4
Alanine Transferase	0-50U/L	37	18	21
Alkaline Phosphatase	30-120U/L	291	346	429
Gamma Glutamyl Transferase	0-38U/L			173
Magnesium	0.73-1.06mmol/L	0.8	0.85	0.89
Inorganic Phosphate	0.81-1.45mmol/L	1.0	1.12	1.03
Erythrocyte Sedimentation Rate	0-20mm/hour		79	
Sputum for AFB direct smears x1 x2 x3		No AFB seen	No AFB seen	No AFB seen
Liver biopsy for TB PCR			Negative	
Liver biopsy for *mycobacterium tuberculous* culture and sensitivity			Negative	
HIV			Negative	
ANA		Negative	Negative	
24 hours urine calcium	0-7.7mmol/L		8.9	
6-minute walking test			Total walking distance= 228 meters, no desaturation, normal recovery	
Lung function test			Severe restrictive pattern with FEV_1 49% and FEV_1/FVC of 0.9	

DISCUSSION

Sarcoidosis has an estimated worldwide prevalence of 2-60 per 100,000 people.[1] It affects all ethnicities especially the Scandinavian and rarely in patients of Chinese and Taiwanese background.[1] There is currently no detailed data on sarcoidosis available in Malaysia. Globally, more females are affected with sarcoidosis compared to males with a peak among the age group around 20-40 years old.[1]

Sarcoidosis is a great mimicker with numerous differential diagnoses including mycobacterium infection, viral, fungal, protozoan, autoimmune diseases, and haematological malignancy. As mycobacterium tuberculosis is more prevalent in Malaysia, often clinicians would have to extensively investigate and rule out tuberculosis prior to confirming sarcoidosis histologically. Table I list the reported sarcoidosis cases in Malaysia published over the last two decades. Among the local cases reported, majority were

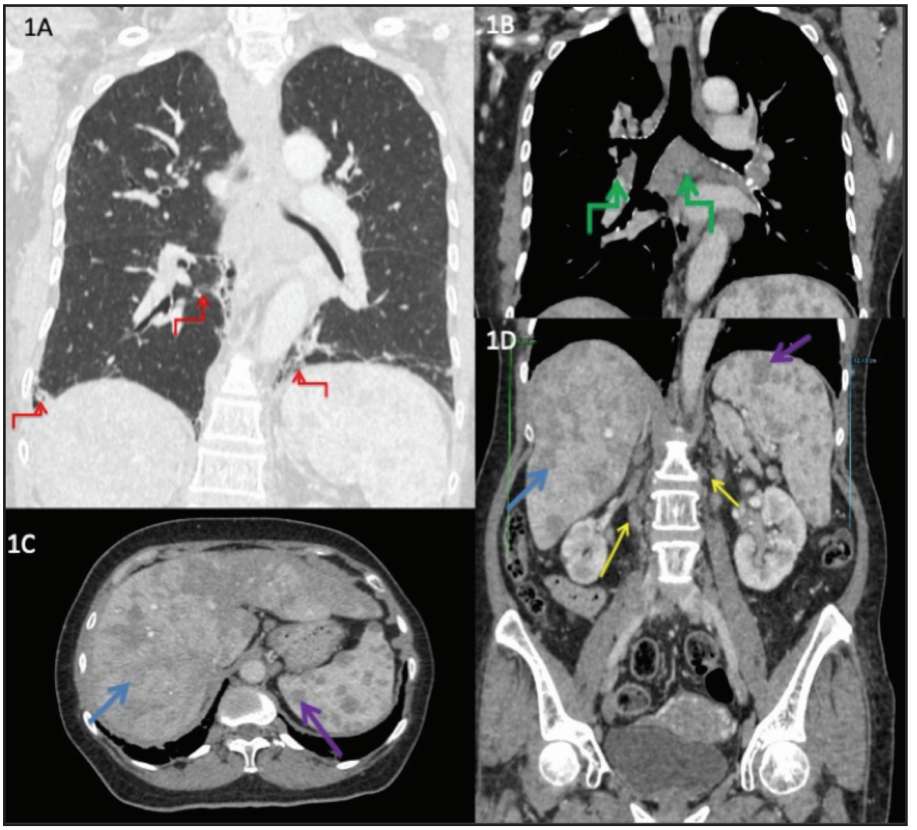

Fig. 1: CT Thorax (coronal view) in mediastinal and lung window. Multiple mediastinal and hilar lymph nodes (green arrows), with no calcification or center necrosis. Fibrosis and early honeycombing changes are also present at the periphery of the lung (red arrows) suggestive of stage 4 pulmonary sarcoidosis. CT Abdomen (mediastinal window) at axial and coronal view. There is diffuse heterogeneous enhancement of the liver (blue arrows) and multiple hypodense nodular lesions scattered in the spleen (purple arrows). Multiple subcentimeter para-aortic lymph nodes are also present (yellow arrows).

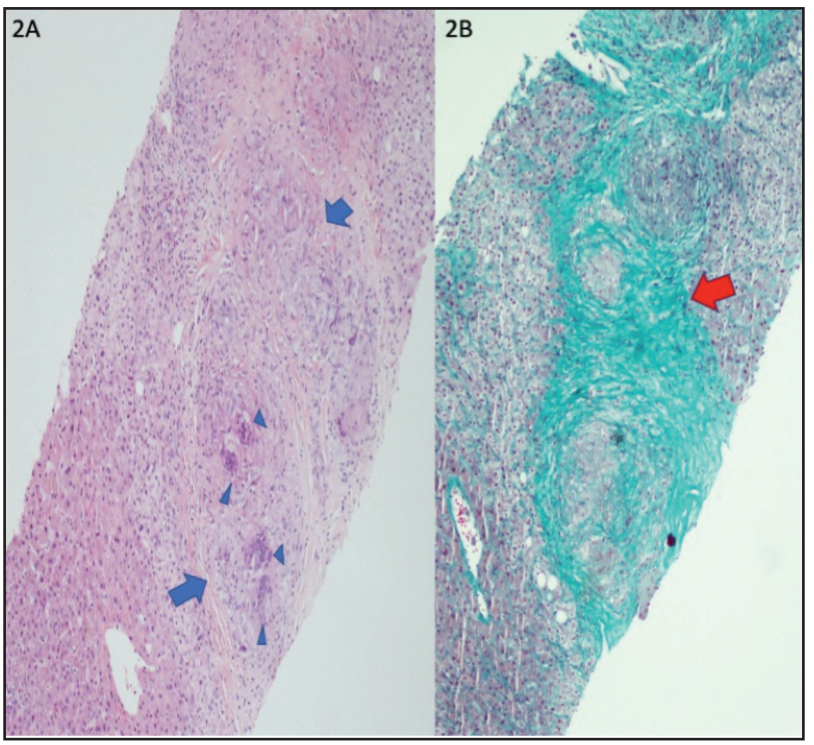

Fig. 2: Hematoxylin-eosin stain revealed multiple epitheloid granulomata (blue arrow) with multinucleated giant cells (blue arrowhead). Masson Trichrome stain revealed epithelioid granulomata surrounded by concentric hyalinized collagen (red arrow).

pulmonary sarcoidosis consistent with reports from international literatures. Most of the local papers described of the difficulty in arriving at the diagnosis of pulmonary sarcoidosis in view of its rarity and the prevalence of tuberculosis in Malaysia. Among the cases reported locally, there were two cases of hepatic sarcoidosis for the past twenty years. Hepatic involvement is seen in around 50% of cases of sarcoidosis as reported but it is rarely here.[7] Most patients are asymptomatic, with around 20% presenting with clinically significant disease.[7] While half of the patients have biopsy-proven hepatic sarcoidosis, approximately 20% had palpable hepatosplenomegaly, 10-30% developed elevated liver enzymes and 15% reported abdominal pain and pruritus.[7] Granulomatous lesions are always found in liver biopsy typically around the portal and periportal zones of hepatic sinuses.[7]

Serum angiotensin converting enzyme is usually elevated but not pathognomonic. Hypercalcemia occurs in 10-20% of patients as seen in our patient, attributed to the overproduction of 1, 25-dihydroxycholecalciferol from activated macrophages.[7]

Our patient was initially treated successfully with steroids when diagnosed with stage II pulmonary sarcoidosis three years ago. However, her disease progressed to stage IV pulmonary sarcoidosis and involved the extrapulmonary sites as she had missed her appointments. Her raised alkaline phosphatase levels had driven the investigation of extrapulmonary sarcoidosis. The American Thoracic Guidelines recommends that in patient with sarcoidosis who have neither hepatic symptoms nor hepatic sarcoidosis, a baseline alkaline phosphatase need to be reviewed as a screening for hepatic sarcoidosis.[1] Patients who are asymptomatic with mild elevations of liver enzymes, and normal synthetic liver function will only require close monitoring without any immunosuppressive agents.[1] Hepatomegaly alone from physical examination or radiographic investigation in the absence of symptoms is not an indication for treatment. In asymptomatic patients, the mild hepatitis often resolves spontaneously or remains stable for years.[1] Our patient did not fulfil the treatment criteria. Generally, the indications to start treatment include being symptomatic, or presence of significant number of granulomas on biopsy. The first line medical therapy is oral prednisolone 0.5mg/kg per day with gradual taper. Corticosteroids reduce the number of hepatic granulomas by suppressing the inflammatory response.[7] Ursodeoxycholic acid can be used to reduce cholestasis by decreasing the biliary secretion of cholic and chenodeoxycholic acids.[7] Second line treatment involves methotrexate.[7] Albeit liver involvement is common in sarcoidosis, end-stage liver disease remains a rare indication for orthotopic liver transplantation. Investigators from the University of Tennessee Health Sciences Center had found statistically significant graft and patient survival on the long-term outcomes of liver transplantation in end stage hepatic sarcoidosis when compared to other cholestatic diseases.[8]

CONCLUSIONS

Sarcoidosis remains idiopathic and heterogenous in manifestations. A suspicion of extrapulmonary sarcoidosis should warrant extensive investigations for associated liver disease, as this may impact on the prognosis. Asymptomatic patients with gastrointestinal sarcoidosis generally do not need treatment. Liver transplantation is a plausible option if there is a risk of progression to end-stage liver disease. Our case illustrates the importance for clinicians to follow up sarcoidosis patients regularly as they may progress to pulmonary or extra-pulmonary sarcoidosis. Hepatic sarcoidosis is rare but remains a common manifestation of extra-pulmonary sarcoidosis and often there are many other differential diagnoses with the similar presentation.

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