Cholestasis with Hepatic Fibrosis secondary to Sarcoidosis - A Case Report

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Sarcoidosis is a chronic granulomatous disease of unknown etiology occurring world wide[1]. The problem of diagnosis of sarcoidosis in a country like Pakistan is two fold: lack of awareness of its existence and difficulty in differentiating it from the highly prevalent tuberculosis with which it shares many clinical and pathological features. It can affect almost any organ. We present a case with one of the rarer manifestations - cholestasis with hepatic fibrosis. To our knowledge this is the first such case being reported from Pakistan.

Case Report

A 64 year old male, retired banker presented in our clinic in May 1999 for evaluation of a 5 year history of weight loss and abnormal laboratory results. He was a known hypertensive. He started noticing weight loss in 1994; over a period of a few months his weight decreased from 55-60 kg to 40 kg. He denied persistent fever, night sweats, cough, shortness of breath, change in appetite, diarrhea, lack of energy, joint pains or skin changes. He spontaneously regained some weight in 1995 and had an extensive work up over.the years as shown in Table 1.

Table1. Haematological, biochemical and radiological investigations.

	CBC				RFT		TFT			Serum Proteins			LFT					
	Hb	Plt	ESR	FBS	BUN	Cr	T3	T4	Urine DR	TP	Alb	Glb	TB	DB	ALT	AP	γGT	MT (5 PPD units)
Aug 94	13.1		61↑	88	10			10.9	normal									
Sep 94			52↑										0.36	0.14	25	182↑	100↑	0 mm (twice)
Nov 94	12.3	↓	50↑							8.3	4.1	4.2↑	0.8	0.0	29	124↑	115↑	
May 95	12.4	192							normal									
June 95	13.7		64↑				1.34	9.3		8.7	4.1		0.8	0.1	31	171↑	173↑	
Dec 95			56↑										0.7	0.1	25	150↑	142↑	
May 96				100	16	1.3			normal									
July 98	13.1	80↓							normal								143↑	

1987	**Xray Chest:** normal
1990	**Xray Chest:** normal
Aug 93	**Xray Chest:** normal
Sept 94	**Xray Chest:** fibrosis both upper zones **Ultrasonography Abdomen:** mild hepatosplenomegaly and cholilithiasis **CT scan Abdomen:** Cholelithiasis with cholecystitis, mild splenomegaly, localized gastric wall thickening **Endoscopy:** Diffuse gastritis in fundus **Hepatitis serology for HBV & HCV**: negative
June 95	**Xray Chest:** fibrosis both upper zones **ANA, ASMA, AMA:** negative

CBC=Complete Blood Count; **RFT**=Renal Function Tests; **TFT**=Thyroid Function Tests; **LFT**=Liver Function Tests; **Plt**=Platelets; **Cr**=Cretinine; **TP**=Total Proteins; **Alb**=Albumin; **Glb**=Globulins; **TB**=Total Bilirubin; **DB**=Direct Bilirubin; **AP**=Alkaline Phosphatase; **MT**=Mountox Test
↓= Decreased, ↑=Increased
Normal values: Plt: 150-450 x 10^9/L, Glb: 1.9-2.8 g/dL, AP: 39-117 U/L, γGT: 11-50 U/L

He had persistently elevated ESR, Alkaline Phosphatase and yGT with negative MT. He denied any previous history of jaundice, blood product transfusion or contact with active TB. He was a non-smoker and was not taking any medicines currently: he had used Beta Blockers and ACEI in the past for his hypertension.

On examination he did not look sick, was anicteric and weighed 45 kg. He had finger clubbing but no evidence of chronic liver disease: the examination of his chest, heart, skin and lymphatic system was normal. He had non-tender hepatosplenoniegaly without ascites or pedal edema. His work up at this stage again showed elevated ESR. Alkaline Phosphatase and yGT with negative MT (Table 2).

Table 2

	CBC				Hepatitis serology		LFT									
	Hb	Plt	ESR	FBS	HbsAg	Anti HCV	TB	DB	ALT	AP	γGT	ANA	Ferritin	Transferrin saturation	ACE level	MT (5 PPD units)
May 99	13	164	100↑	97	-ve	-ve	0.8	0.25	26	249↑	146↑	-ve	150	34.9%	70	0 mm

X-ray Chest: fibrosis both upper zones (unchanged from previous X-rays)
Sputum for AFB (3 sets): negative
Ultrasonography Abdomen: Suggestive of portal hypertension
Magnetic Resonance Cholengio-Pancreatography (MRCP): No dilated intrahepatic or extrahepatic ducts
High Resolution CT Scan (HRCT): Bilateral interstitial fibrosis, bronchiectasis both lower lobes (Fig. 1)

An HRCT of the chest confirmed diffuse interstitial disease (Figure 1).

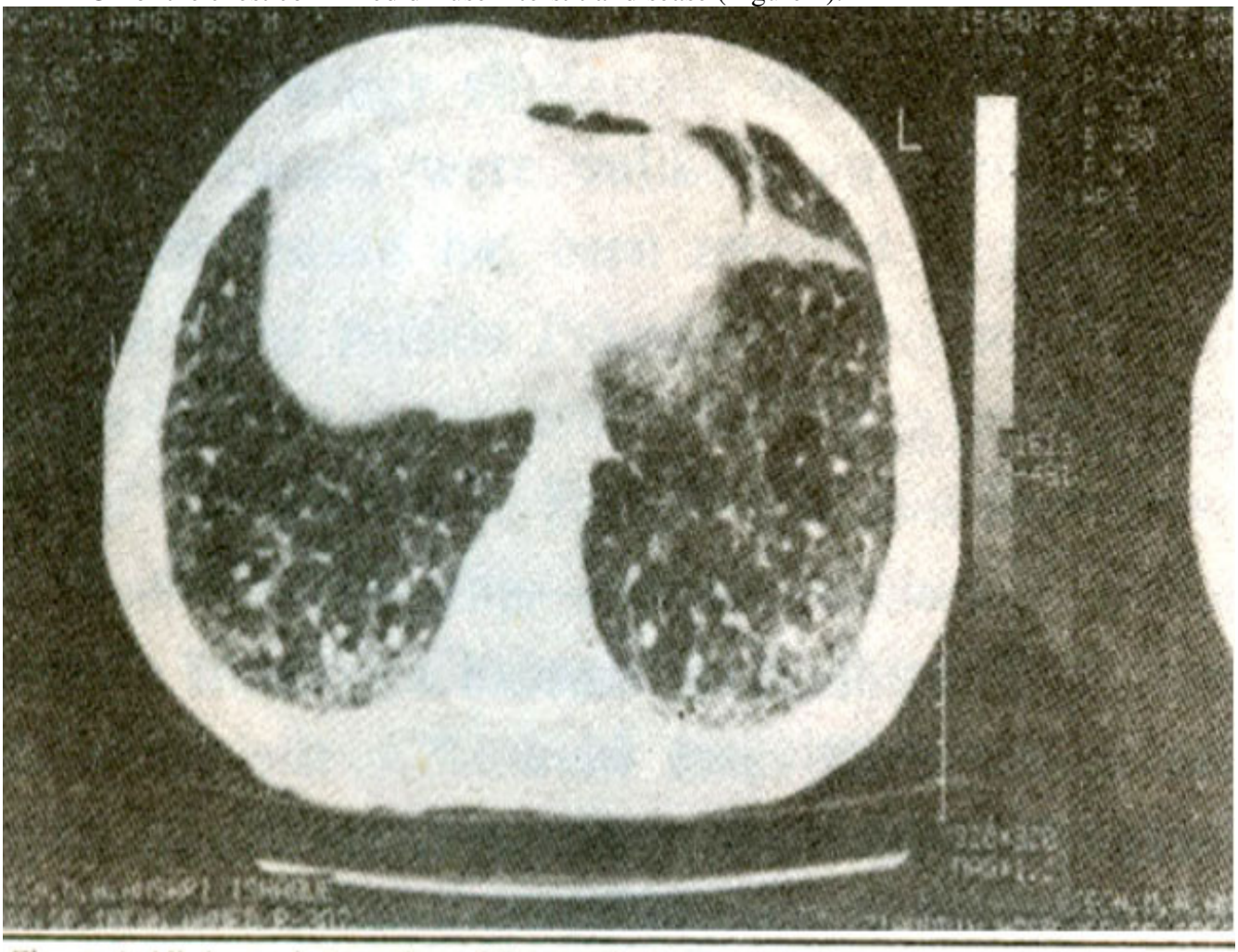

Figure 1. High resolution chest CT near the base of the lungs showing diffuse reticulo-nodular Shadows, fibrosis and bronchiectasis

A needle biopsy of the liver was performed which showed chronic portal inflammation with piecemeal necrosis and granuloma formation (Figure 2)

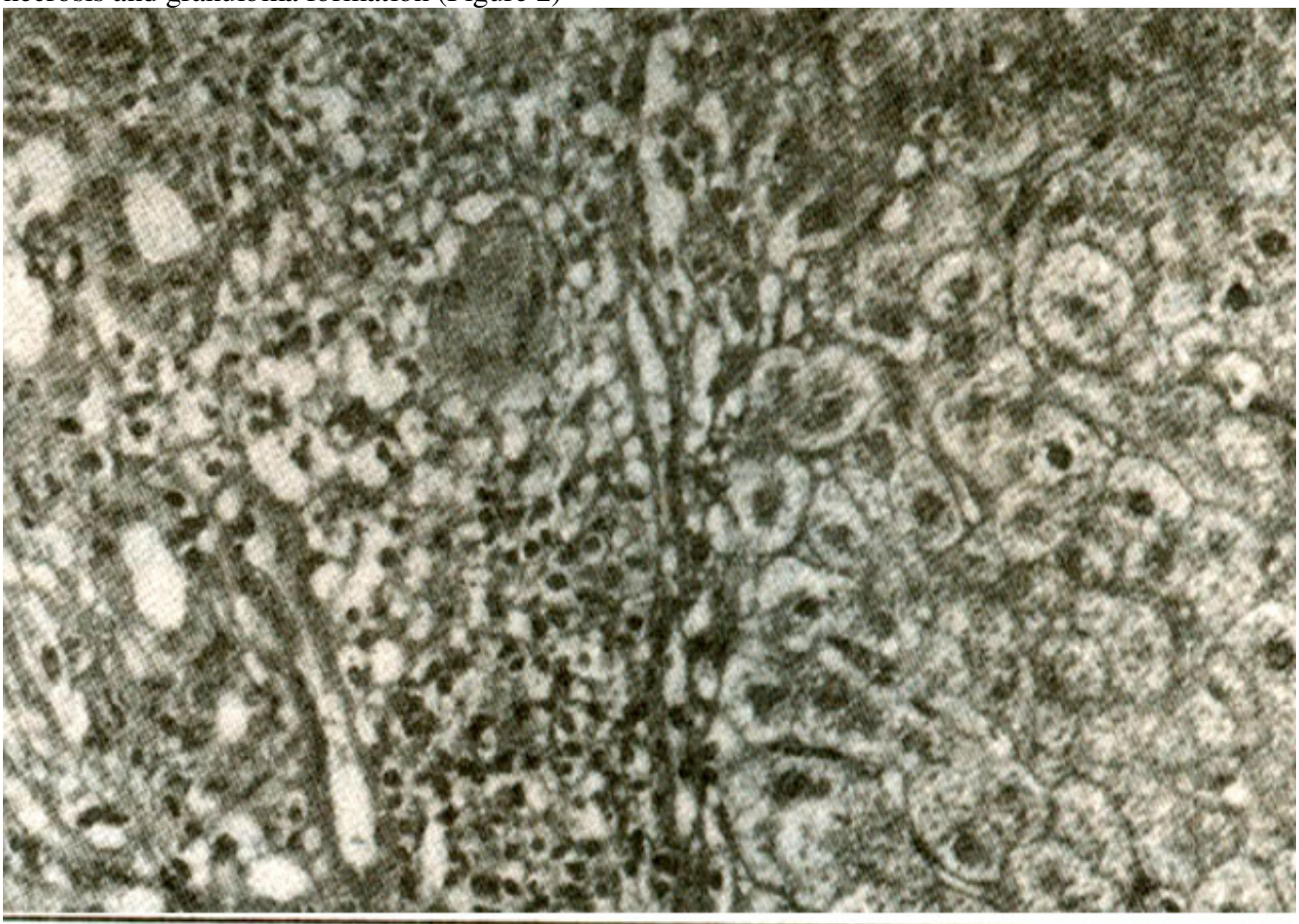

Figure 2. Section of a liver biopsy specimen showing both diffuse and granulomatos chronic portal inflammation, a Langhans giant cell can also be seen (HE stain x 100)

A diagnosis of Hepatic Sarcoidosis was made and he was started on systemic steroids.

Subsequent Course

Despite his previous denial of any constitutional symptoms lie started feeling much better and his weight increased to 50.5 kg. His ESR (9mm) and Alkaline Phosphatase (104 IU) - though not his yGT - declined rapidly to normal. Interestingly he noticed that lie found it much easier to button his clothes now. He had developed difficulty with this task about 3 years ago, had a normal nerve conduction study and then forgotten about it. He only recalled it now when he noticed a sudden improvement. The possibility of sarcoid peripheral neuropathy can not be ruled out.

Discussion

Diagnosis of sarcoidosis (of any organ) is essentially a diagnosis of exclusion[1] there are no pathognomomic tests. Elevation of serum ACE (SACE) level (normal value 8-52 U/L) is only useful when either it is normal (high negative predictive value) or markedly elevated i.e. > 100 U/L (high positive predictive value)[2]. Kviem-Siltzbach test has a sensitivity greater than 60%[3] and specificity approaching 95%[4] hut the material is not easily available and the test is not recommended[1]. Asymptomatic, clinically insignificant hepatic granulornas are very common in sarcoidosis with an

incidence of 40-70%[1,5]. When clinically significant liver involvement occurs, there are usually three well recognized patterns: chronic intrahepatic cholestasis, portal hypertension and Budd-Chiari Syndrome[5]. Ilepatic granulomas have a broad differential diagnosis (Table 3).

Table 3. Causes of hepatic granulomas*.

Infections	Systemic disease
Bacterial	Sarcoidosis
Tuberculosis	Hodgkin'sandnon-Hodgkin's
Mycobacterium avium intracellulare	lymphoma
Brucellosis	Primary Biliary Cirrhosis
Leprosy	Crohn's disease
	Wegner's granulomatosis
Viral	Granulomatous hepatitis, idiopathic
EpsteiBarr virus	Whipple's disease
Cytomegalovirus	Primary Sclerosing Cholingitis
Chicken pox	**Drugs**
AIDS	Allopurinol
Protozoal & Helminthic	Carbamazipine
Schistosomiasis	Isoniazid
Ascariasis	Phenylbutazone
Toxocariasis	Quinine
Toxoplasmosis	Sulphonamides
Fungal	**Others**
Histoplasmosis	Intra-abdominal neoplasms
Coccidioidomycosis	Beryllium
Blastomycosis	Cement
Rickettsial	Copper
Q fever	Mica dust
Spirochetes	Mineral Oil (Lipogranulomas)
Syphilis	

* compiled from various sources

In a small series of' hepatic granulomas reported from Pakistan, the incidence of sarcoidosis was

7,4%[6]. in a similar series of 88 cases from USA. the incidence of sarcoidosis was 22%[7].
Although no bacterioIogical cultures were done in our patient. we made the diagnosis of sarcoidosis on the basis of the features of a systemic disease with weight loss, diffuse lung involvement with persistently negative PPD reaction and repeatedly negative AF'B smears, an elevated SACE level with cholestatic granulomatous liver disease in the absence of an alternative diagnosis (negative ANA, AMA, SMA, HBV and HCV serology and absence of evidence of hemochromatosis). We did not perform AFB culture (a test with low sensitivity) and ANCA-P to rule out Primary Sclerosing Cholangitis (in view of lack of Magnetic Resonance Cholangiopancratography or pathology findings suggesting this diagnosis). Other infectious causes were unlikely on clinical grounds. Sarcoid cholestasis has been reported frequently in the literature from outside Pakistan[8-10]. Necroinflammatory changes (as seen in our patient) have been reported in up to 41% of the patients[9]. Hepatic fibrosis has also been described[9,11]. The other common cholestatic diseases -Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis - may both be associated with granuloma formation; the differentiation from sarcoidosis may be difficult and is based on other clinical features, serology and Kviem Test[3,12] ; in fact an overlap syndrome of Primary Biliary Cirrhosis and Sarcoidosis has been suggested,[3]. Although involvement of the lung and hilar nodes has been the most common presentation of sarcoidosis in Western patients, a number of studies have indicated ethnic variations in the severity and pattern of organ involvemen[14-18]. The pattern of organ involvement in sarcoidosis and especially the prevalence of clinically significant hepatic disease in Pakistani population remains unknown.
Systemic steroids are the mainstay of active, systemic sarcoidosis especially in patients with clinical variables associated with poorer prognosis: Black race, onset after age 40 years, symptoms present for more than 6 months, absence of Erythema Nodosum, splenomegaly, involvement of more than three organ systems and stage Ill pulmonary disease[19,20]. Our patient had several of these features. Steroids improve the clinical and biochemical features without evidence of benefit for the long term outcome[21]; they do not reverse the fibrosis[22]. Several other drugs have been anecdotally reported as useful including Methotrexate and Cyclosporine' .Chloroquin has been used as steroid sparing drug in Hepatic Sarcoidosis with some success[23].
Our patient was symptomatic with cholestatic sarcoidosis for five years before the diagnosis. This highlights the importance of considering sarcoidosis in the differential diagnosis of chronic cholestasis with systemic features.

References

1.Newman IS. Rose CS, Maier LA. Sarcoidosis. N Engl J. Med., 1 997;336 1224.32
2.Khan AH, Ghani F, Khan A, et al. Role of Serum Angiotensin Converting Enzyme in Sarcoidosis. JPMA 1998:48:131-3.
3.Eklund A, Stjernberg N, Uddenfeldi P. et al. Kveim test and mitochondrial antibodies in the differential diagnosis between primary biliary cirrhosis and sarcoidosis. Sarcoidosis, 1985:2:38-41.
4.Harrison's Principles of Internal Medicine. 14th Edition. Singapore, McGraw Hill Inc., 1998,p.1927.
5.James DO, Sherlock S. Sarcoidosis of the liver. Sarcoidosis, 1994;11:2-6
6.Sheikh S, Shaikh RB, Rab SM. Granulomatous hepatitis: Analysis of twenty seven patients. JCPSP.. 1997; 7:235-36.
7.Sartin iS, Walker RC. Granuloinatous hepatitis: a retrospective review of 88 cases at the Mayo Clinic. Mayo. Clin. Proc., 1991;66:914-8.
8.Bass NM, Burroughs AK, Scheuer PJ, et al. Chronic intrahepatic cholestasis due to sarcoidosis. Gut, 1982:23:417-21.
9.Devaney K, Goodman ZD, Epstein MS, et al. Hepatic Sarcoidosis. Clinicopathologic features in 100

patients Am. i. Surg. Pathol., 1993;1 7:1272-80.
10.Rudzki C, Ishak KG, Zimmerman HJ. Chronic intrahepatic cholestasis of sarcoidosis. Am. J. Med., 1975:59:373-87.
11.Kitamura Y, Motoi M, Terada 1. An autopsy case of ancient sarcoidosis associated with severe fibrosis in the liver and heart Pathot. Int., 1998;48:536-41.
12.Ludwig J, Colina F, Poterucha JJ. Granulomas in primary selerosing cholangitis. Liver. 1995:15:307.12.
13.Keffe EB. Sarcoidosis and primary biliary cirrhosis. Literature review and illustrative case. Ant. J. Med., 1987;83:977-80.
14.Rybicki BA, Major M,Popovich J et al. Racial ditierences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am. J. Epidemiol., 1997:145:234-41 -
15.Mayock RL, Bertrand P, Morrison CE. el al. Manifestations of sarcoidosis: analysis of 145 patients, with a review of nine series selected from the literature. Am. 3. Med.,1963:35:67-89.
16.Keller AZ. Hospital, age, racial, occupational, geographical, clinical and survivorship characteristics in the epidemiology of sarcoidosis. Am. J. Epidemiol., 1971:94:222-30.
17.Siltzbach LE, James DG. Neville F. et al. Course and prognosis of sarcoidosis around the world. Am. J. Mcd, 1974:57:847-52.
18.Edmondstone WM, Wilson AG, Sarcoidosis in Caucasians, Blacks, and Asians in London, Br. J. Dis. Chest, 1985:79:27-36.
19.Mana 3, Salazar A. Manresa F. Clinical factors predicting persistence of activity in sarcoidosis: a multivariate analysis of 193 cases. Respiration, 1994:61:219-25.
20.Takada K, Ina Y, Noda M. The clinical course and prognosis of patients with severe, moderate or mildsarcoidosis. J. Clin. Epidemiol., 1993,46:359-66.
21.Du Bois RM. Corticosieroids in sarcoidosis friend or foe? Eur. Respir. J., 1994:7:1203-9.
22.Shelock, S. Dully, 3. Diseases of the liver and biliary system. 9th Edition 1993. Blackwell Scientific Publications.
23.Galwanker S. Was M, Desai D, et al, Hepatic sarcoidosis responding to chloroquine as steroid-sparing drug. Indian 3. Gastroenterol., 1999:18:177-8. 1998;48:536-41.