ORIGINAL ARTICLE

Study of Liver Dysfunction in Pulmonary Tuberculosis Patients

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ABSTRACT
BACKGROUND: Pulmonary tuberculosis is found to be associated with impaired liver function tests. **AIMS & OBJECTIVES:** Study of 30 cases of pulmonary tuberculosis in which liver function tests were carried out. **MATERIALS & METHODS:** After confirming the presence of AFB, Liver function tests and Liver biopsy were done. **OBSERVATIONS:** H.P.E. of liver revealed tuberculous granuloma in one case (3.33%) while 70% showed non-specific changes. However, 26.6% were normal. **CONCLUSION:** Granuloma formation is rare and liver biopsy can hardly be useful as a routine procedure to rule out T.B. in doubtful cases of systemic tuberculous infections.

Key Word: Symptomatology, Smoking, GI system, Liver enlargement, Albuminuria

INTRODUCTION

The liver being always on the edge of safety happens to suffer indirectly from the disease of other organs. It has been a frequent observation that pulmonary tuberculosis is found to be associated with impaired liver function tests.

Hepatic damage is a frequent finding at autopsy in tuberculosis; while clinical manifestations of liver involvement in pulmonary tuberculosis is rare. No doubt the enormous reserve power of liver is responsible for this aspect. Although clinical evidence points to a lack of significant hepatic damage; sensitive liver function tests together with biopsy studies indicate otherwise.

Of many diseases capable of producing granulomatous lesions in liver, tuberculosis forms one of the important causes. By virtue of its large number of mononuclear phagocytic cells and strategic location, liver clears many substances off circulation including microorganisms, antigens, immune complexes and toxins.

The liver being highly vascular, a haematogenous spread of infection is expected early in course of tuberculosis.

However the involvement of liver in pulmonary tuberculosis patients is variable.

In pyrexia of unknown origin, the importance of liver biopsy is stressed; and according to Harrison[7]; a number of cases turned out to be granulomatous tuberculous lesions. This proves the importance of liver function studies in cases of tuberculosis.

AIMS & OBJECTIVES

The patients of pulmonary tuberculosis often found to have associated systemic manifestations like anemia, hypoproteinemia etc. On investigations; liver functions of these patients found to have deranged. When treated with AKT; liver functions are altered at least in some; where again the drugs are blamed. So we thought of assessing the liver in general in pulmonary tuberculosis. The aims and objectives of study were:

- To study the manifestation of pulmonary tuberculosis in liver.
- To study the liver functions in pulmonary tuberculosis.
- To study the liver functions in pulmonary tuberculosis during drug administration.

The present series includes a study of thirty cases of pulmonary tuberculosis, in

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which liver function tests along with liver biopsy were carried out.

MATERIALS & METHODS

The present study comprises of thirty cases of pulmonary tuberculosis. The patients were admitted to the tuberculosis ward of LG Hospital, Ahmedabad; from 1st January 2016 to 15th October 2016. They were all in age group of 19-65 years and all were males except one female. The diagnosis in each case was confirmed by clinical, bacteriological and roentgenographic procedures. Cases with extrapulmonary involvement were excluded from study. Diseases like Diabetes Mellitus, Nephrotic Syndrome, cases with ascites and edema were also excluded because of the likelihood of hepatic changes that can occur with above mentioned conditions.

On the day of admission, routine history physical examination, blood counts, erythrocyte sedimentation rate and urine examination were done. All the cases were X-rayed (X-ray chest PA view) at the time of admission and sputum for AFB (overnight sputum) were done consecutively for 3 days. After confirming the presence of acid fast bacilli, following liver function tests were done: serum bilirubin, SGPT, SGOT, serum alkaline phosphatase, total plasma proteins, serum albumin, serum globulin, Albumin-Globulin ratio and serum cholesterol. Along with this, bleeding time, clotting time, prothrombin time, blood grouping and HBsAg were also performed.

After getting the report of investigations, liver biopsy was done using Vim-Silvermans cutting needle. In cases of high value of bleeding time, clotting time and prothrombin time, injection Vitamin-K had been given and BT, CT and PT were repeated. Vitamin-K activates an enzyme system in liver endoplasmic reticulum which catalyses gamma carboxylation of selected glutamyl residues in clotting factor precursors. The gamma carboxylation enhances Ca^{+2} and phospholipid binding capacity of prothrombin and permits its rapid conversion to thrombin in the presence of factors V and X. When all the values were normal, the patient was taken for liver biopsy after sending the blood for grouping and cross-matching.

Procedure

- **Pre-anaesthetic Medication:** Injection 0.6mg of atropine and injection phenobarbitone 50mg were given intramuscularly half an hour before the procedure.
- **Position:** Patient lies on his back in the bed with right side very near to the edge of the bed.
- **Site:** Either ninth or tenth intercostals space in the mid axillary line was selected always. The area is sterilized with cetavlon, iodine and spirit.
- **Local Anaesthesia:** The skin, subcutaneous tissue and tissues upto the capsule of liver are infiltrated with 1% lignocaine.
- **Biopsy:** This was done using Vim-Silvermans needle.
- **Seal:** After biopsy the punctured skin is sealed with tincture benzoin.

During the post procedure period, pulse, respiration, temperature and blood pressure were recorded hourly for the first four hours and then fourth hourly for 24 hours.

The biopsy material was taken to pathology department and H.P.E. done. The reports were given only after looking through many fields from the best prepared slide.

Pathological extent of Pulmonary Tuberculosis: This classification was according to the National Tuberculosis Association 1968- U.S.A.

- **Minimal lesion:** Those which are slight to moderate density but without demonstrable cavity. The total extent regardless of distribution should not exceed one zone on one side.
- **Moderately advanced:** The total extent of the lesion, regardless of the distribution should not exceed one-third (1/3) volume on one side. Total diameter of cavitation if present must be less than 4cm in standard roentgenogram.
- **Far advanced:** Lesions more extensive than moderately advanced.

PROFORMA

1. Name:
2. Age:
3. Sex:
4. Reg. No.:
5. Occupation:
6. Address:
7. Presenting Complaints:
8. Past History:
- Amoebiasis
- Jaundice
- Hypertension
- Blood disorders
- Abdominal procedures
- Others

9. Personal History:
- Alcoholism
- Smoking
- Drug history
- Others

10. General Examination:
- Pulse
- Blood pressure
- Temperature
- Respiratory rate

11. Respiratory System:
12. Gastrointestinal System:
13. Cardiovascular System:
14. Weight:
15. Sputum:
- Positive/Negative
- Culture if any

16. X-ray:
- Unilateral/Bilateral
- Cavitory/Non-cavitory
- Disseminated T.B., Miliary T.B.
- Plain AXR for calcified liver foci, mesenteric glands and associated shadows

17. Blood:
- Hb
- TC
- DC
- ESR

18. LFT:
- Serum Bilirubin: Direct, Indirect
- SGPT
- SGOT
- Serum alkaline phosphatase
- Serum cholesterol
- Serum proteins: Total, Albumin, Globulin, A/G ratio

19. BT, CT, PT
20. HBsAg
21. Blood grouping
22. Liver biopsy

OBSERVATIONS

Table 1: Showing Age and Sex distribution of cases

Age groups (in years)	No. of cases	Sex				Total %
		Male		Female		
		No.	%	No.	%	
<20	3	3	10.00	-	-	10.00
21-30	11	10	33.34	1	3.33	36.67
31-40	6	6	20.00	-	-	20.00
41-50	7	7	23.33	-	-	23.33
51-60	1	1	3.33	-	-	3.33
>60	2	2	6.67	-	-	6.67
Total	**30**	**29**	**96.67**	**1**	**3.33**	**100.00**

Out of thirty cases, 3 (10%) were in the age group of less than 20, 11 (36.67) in 21-30 group, 6 (20%) in 31-40 group, 7 (23.33) in 41-50 group, 1 (3.33%) in 51-60 group and 2 (6.67%) in above 60 group.

Majority of cases were belonging to the age group of 21-50 (80%). Youngest was 19 year old and oldest 65 year. All the patients except one were males.

Table 2: Showing nature of Occupation

	Nature of Occupation	No. of cases	Percentage
1.	Sedentary work	8	26.67
2.	Moderate work	12	40.00
3.	Hard work	10	33.33
	Total	**30**	**100.00**

8 patients (26.67%) were doing sedentary work, 12 (40%) were doing moderate work and 10 (33.33%) hard work.

Table 3: Showing Residential Distribution

Residential area	No.	Percentage
Slum	6	20.00
Rural	6	20.00
Sub-Urban	5	16.67
Urban	13	43.33
Total	**30**	**100.00**

Out of thirty cases, 6 (20%) were belonging to slum and rural areas each, 5 (16.67%) to semi-urban and 13 (43.33%) to urban area.

Table 4: Showing Spectrum of Symptomatology

Symptoms	No. of cases	Percentage
Cough	27	90.00
Expectoration	21	70.00
Fever	19	63.33
Breathlessness	16	53.33
Chest Pain	4	13.33
Haemoptysis	5	16.67
Weakness	7	23.33

Anorexia	5	16.67
Abdominal Pain	2	6.67
Miscellaneous (Hoarseness, Dysphagia)	3	10.00

The spectrum shows that maximum no. of patients 27 (90%) exhibited cough, expectoration by 21 (70%), fever by 19 (63.33%) and breathlessness by 16 (53.33%) patients. Very few patients had haemoptysis (16.67%), weakness (23.33%), anorexia (16.67%) and abdominal pain (6.67%).

Table 5: Showing Prevalence in Smokers

Personal History	No. of cases	Percentage
Smokers	14	46.67%
Non-Smokers	16	53.33%
Total	**30**	**100.00%**

Above table shows 14 patients (46.67%) gave positive history of smoking while rest 16 (53.33%) were non-smokers. Among smokers one patient was alcoholic too.

Table 6: Showing Gastrointestinal Tract involvement

GIT	No. of cases	Percentage
Hepatomegaly	9	30
Splenomegaly	0	0
Ascites	0	0
Others	0	0
Normal	21	70
Total	**30**	**100**

9 cases (30%) showed liver enlargement of liver from 1-7 cm. All others were normal.

Table 7: Showing Radiological extent of disease

Extent of lesion	No. of cases	Percentage
Minimal	1	3.33%
Moderately advanced	2	6.67%
Far advanced	27	90.00%
Total	**30**	**100.00%**

Only 1 case (3.33%) had minimal lesion and 2 cases (6.67%) had moderately advanced lesion. Majority were belonging to far advanced groups (90%).

Out of 9 cases showing liver enlargement, all were from the 27 far advanced group and 1 each from the other two groups.

Table 8: Showing Serum Glutamic Pyruvic Transaminase (S.G.P.T) level

S.G.P.T.	No. of cases	Percentage
Abnormal (>40 KARMEN UNITS)	3	10
Normal (<40 KARMEN UNITS)	27	90
Total	**30**	**100**

The above table shows that in 27 cases (90%), SGPT was normal while only in 3 cases (10%), SGPT showed a rise from normal range of 0-40 KARMEN UNITS (I.U.).

Table 9: Showing Serum Glutamic Oxalo Transferase (S.G.O.T.) levels

S.G.OT.	No. of cases	Percentage
Abnormal (>40 KARMEN UNITS)	1	3.33
Normal (<40 KARMEN UNITS)	29	96.67
Total	**30**	**100**

Only 1 case (3.33%) showed an increase in SGOT level. Rest 96.67% were in normal range.

Table 10: Showing Serum Alkaline Phosphatase levels

S.Alk Phosphatase	No. of cases	Percentage
Abnormal (>3-13 K.A. UNITS)	8	26.67
Normal (3-13 K.A. UNITS)	22	63.33
Total	**30**	**100**

The study showed that 8 cases (26.67%) had an increase in S.Alk phosphatase levels while rest 63.33% were in normal range of 3-13 King Armstrong Units.

Table 11: Showing Serum Cholesterol levels

S. Cholesterol	No. of cases	Percentage
Hypocholesterolaemia (<150 mg %)	5	16.66
Normal (150-250 mg %)	25	83.33
Total	**30**	**100**

5 cases (16.66%) showed hypocholesterolaemia while remaining 25 cases (83.33%) were having serum cholesterol in normal range. None of the cases showed hypercholesterolaemia i.e. >250 mg % serum cholesterol.

Table 12: Showing Total Serum Protein content

S. Protein	No. of cases	Percentage
Hypoproteinemia (<5 gm %)	4	13.33
Normal protein (>5 gm %)	26	86.67
Total	**30**	**100.00**

Hypoproteinemia was seen in 4 cases while all others were in normal range.

Table 13: Showing Serum Albumin levels

S. Albumin	No. of cases	Percentage
<3 gm %	9	30
>3 gm %	21	70
Total	**30**	**100**

Taking the lower limit of normal serum albumin content as 3 gm %, 9 cases (30%) showed hypoalbuminaemia. Rest 70% had normal albumin levels.

Table 14: Showing Serum Globulin levels

S. Globulin	No. of cases	Percentage
>3.5 gm %	6	20
<3.5 gm %	24	80
Total	**30**	**100**

Taking the upper limit of normal serum globulin level as 3.5 gm %, 6 cases (20%) showed hyperglobulinaemia. Rest 80% had normal globulin levels.

Table 15: Showing Albumin-Globulin ratio

A/G Ratio	No. of cases	Percentage
Abnormal	23	76.67
Normal (1.8-1.2:1)	7	23.33
Total	**30**	**100**

Considering the standard A/G ratio as 1.8-1.2:1, we found that 23 cases (76.67%) were abnormal, which includes a reversal of A/G ratio in 15 cases (50%). Only 7 cases had normal A/G ratio.

Table 16: Showing Comparison of patients prothrombin time with normal control

Prothrombin time	No. of cases	Percentage
Normal (<4sec difference from control)	16	53.33
Abnormal (>4 sec)	14	46.67
Total	**30**	**100**

Above table shows the increase in Prothrombin time when compared to control. A difference of upto 4 seconds was considered normal. 16 of 30 cases were in the normal range while 14 cases were abnormal.

Table 17: Criteria for Derangement of Liver Function Tests

Tests	Normal values
Serum Bilirubin mg %	0-1
SGPT (KARMEN UNITS)	0-40
SGOT (KARMEN UNITS)	0-40
Serum Alkaline Phosphatase K-A units	3-13
Serum Cholesterol mg %	150-250
Total Serum Proteins gm %	5
Serum Albumin gm %	3
Serum Globulin gm %	3.5
A/G Ratio	1.8-1.2:1
Prothrombin time (seconds)	Upto 4 sec diff from control

Table 18: Showing Comparative study among Liver Function Tests

No.	Liver Function Tests	Nature of abnormality	No. of abnormal cases	Total no. of cases	Percentage of abnormality
1	Serum Bilirubin	Increase	0	30	0.00
2	SGPT	Increase	3	30	10.00
3	SGOT	Increase	1	30	3.33
4	Serum Alkaline Phosphatase	Increase	8	30	26.67
5	Serum Cholesterol	Decrease	5	17	29.41
6	Total Serum Proteins	Decrease	4	30	13.33
7	Serum Albumin	Decrease	9	30	30.00
8	Serum Globulin	Increase	6	30	20.00
9	A/G Ratio	Reversal	23	30	76.67
10	Prothrombin time	Increase	14	30	46.67

The above table shows the percentage of abnormality in liver function tests. Here A/G ratio shows the maximum (76.67%) and serum bilirubin the minimum (0%) abnormality among cases. Investigations like prothrombin time, serum albumin, serum cholesterol and serum alkaline phosphatase showed moderate abnormality while serum globulin, serum total protein, SGPT and SGOT showed mild to moderate derangement.

Table 19: Showing Correlation of Liver Functions with the Radiological extent of the disease.

Radiological extent of the disease		LFT's
Far Advanced	Number	27
	Abnormal percentage	97.89%
Moderately Advanced	Number	2
	Abnormal percentage	6.56%
Minimal lesion	Number	1
	Abnormal percentage	1.47%

The above table shows the percentage of abnormal liver function tests in various groups like minimal lesion, moderately advanced and far advanced. It is seen that liver function tests are more deranged in far advanced group. However an intergroup comparison is not worthwhile here as only one and two cases are present in minimal and moderately advanced group respectively.

Table 20: Showing Albuminuria

Urine	No. of patients	Percentage
Albumin present	12	40
Normal	18	60
Total	**30**	**100**

Routine urine examination exhibited albumin in 12 cases (40%). Sugar was not detected in any of the case as the study excluded the possible diabetics.

Table 21: Showing Liver biopsy results

HPE changes	No. of cases	Percentage
Specific changes	1	3.33
Non-specific changes	21	70.00
Normal	8	26.67
Total	**30**	**100.00**

H.P.E. of liver revealed specific change like tuberculous granuloma in one case (3.33%) while most of the specimens (70%) showed non-specific changes.

However 8 liver tissues (26.67%) were normal.

Table 22: Showing Histological changes in liver

Histological Change	No. of cases	Percentage
Specific:		
Granulomatous lesions	1	3.33
Non-Specific:		
Cellular collections	8	26.67
Focal parenchymal necrosis	5	16.67
Kupffer cell hypoplasia, Dilated sinusoids, R.E. cell hyperplasia	8	26.67
Fatty infiltration	5	16.67
Fibrotic changes, Cirrhosis (4+1)	5	16.67
Amyloid deposit	Nil	-
Normal	8	26.67

The above table shows:

- Only 1 case (3.33%) showed granulomatous change with tubercles.
- Cellular collections were found in 8 cases (26.67%).
- Focal parenchymal necrosis was present in 5 cases (16.67%).
- Kupffer cell hypoplasia, dilated sinusoids, R.E. cell hyperplasia together accounted for 5 cases (16.67%).
- Fatty infiltration was detected in 5 cases (16.67%).
- Fibrotic changes were observed in 4 cases (13.33%).
- Cirrhosis was seen in 1 case (3.33%) only.
- None of the cases exhibited amyloidosis.
- Eight cases were normal (26.67%).

DISCUSSION

In the study of hepatic changes in pulmonary tuberculosis, abnormal liver functions have been reported by various workers and there is a wide difference between the individual reports. From the perusal of their reports, it seems that some evidence of functional hepatic damage was detected in a substantial proportion of tuberculous patients.

Age: In the present series, 30 cases are included in which liver functions as well as histology were studied. In this series maximum no. of cases was from 21-50 age group (Table No.1). Youngest was 19 and oldest was 65 years old. We routinely never admit children in our wards. The age group shows the prevalence of post-primary tuberculosis in general population. All the patients except one (aged 25) were males.

Occupation: In the present study, the majorities of patients (Table No.2) were doing moderate work (40%) and hard work (33%). We could not establish any correlation between the nature of work and changes in liver. In our study, all the 8 normal liver belonged to moderate workers and hard workers, whereas surprisingly, the lone case of granuloma emerged from a sedentary worker. L.F.T also could not produce any relationship over the nature of work.

Residential area: The maximum no. of patient were urban dwellers (43.33%) (Table No.3). This is because our hospital is situated in a city which covers more than 10 lakh population. Involvement of liver was equally distributed among all the population irrespective of their residence.

Symptomatology: In the final analysis of symptoms, the four commonest symptoms in present study were cough (90%), expectoration (70%), fever (63.33%) and breathlessness (53.33%). Anorexia and abdominal pain which are more suggestive of GIT involvement were only 16.33% and 6.66% respectively (Table No.4). This showed that the complaint of respiratory system due to pulmonary tuberculosis is manifested earlier than abdominal symptoms.

Smoking: On interrogating the patients, it was seen that 14 of them (46.67%) were habituated to smoking. Among the smokers, one patient was taking alcohol regularly and on examination showed an enlargement of liver (7cm). On HPE this case turned out to be cirrhotic. As a whole, smoking didn't have any relationship with liver involvement in pulmonary tuberculosis.

GI system: On examination of gastro-intestinal system in detail, it was found that 9 patients had enlarged liver (Table No.6) varying from 1-7cms. Splenomegaly was not seen; may be because miliary tuberculosis was not seen in a single case. We had avoided cases of ascites to make sure that the involvement of liver is only due to pulmonary tuberculosis and not due to abdominal tuberculosis or its other causes. The relative high incidence of hepatomegaly (30%) may be due to

inclusion of certain cases which showed hepatomegaly to assess the histopathological pattern in liver.

Liver enlargement: Mukherjee et al[14] (1968) showed maximum incidence of hepatic enlargement (41.02%). Prasanna et al[17] (1983) showed least incidence of hepatic enlargement (13%). However the present series (30%) comes in between these studies.

Albuminuria: On routine investigation, Albuminuria was found in 40% cases (Table No.20). As we excluded the cases of nephrotic syndrome, ascites etc. which may cause some changes in liver, the cause of abnormality in urine was clearly not known. However the usual causes of albumin in urine are amyloidosis, renal tuberculosis, streptomycin toxicity, fever and toxemia which are commonly seen in tuberculosis. Causes unrelated to tuberculosis like renal vein thrombosis cannot be excluded. Investigations to rule out renal T.B. were not carried out due to unavoidable reasons.

Radiological extent & liver enlargement: According to classification of National Tuberculosis Association, 1968, USA, we radiologically classified our cases. Out of 30 cases, 90% are in far advanced group, 6.67% in moderately advanced and 3.33% in minimal lesion group.

While comparing the extent of pulmonary tuberculosis with hepatic enlargement, it is seen that 7 cases were in far advanced group and one each in moderately advanced and minimal lesion group. The lone case of liver enlargement in lone case of minimal lesion group is because of the admission of that patient to study histopathology. This case on HPE exhibited cirrhotic change and on follow up showed some improvement with anti-tuberculous drugs. The very same patient was taking alcohol for quite some time; so we were in doubt about the etiology. But as this case was responding to treatment, we included this also in our study.

No. of cases in moderately advanced and minimal lesion group is so negligible that no correlation can be judged between radiological extent and liver changes. The available literatures did not show any correlation with radiological extent and liver enlargement.

Serum Bilirubin: In the present series, none of the cases showed an increase in serum bilirubin. Among various workers in this field, the opinion varies. The present series is in full agreement with Bindra Ban[3] (1955), Mittal et al[12] (1965) and Bowry et al[4] (1970) which showed 0.00% abnormal s.bilirubin percentage each. High results are quoted by other workers like Guckian and Perry (1966), Munt (1972) and Jha et al[9] (1974) which showed abnormal s.bilirubin percentages of 50%, 23.7% and 32% respectively. Lichtman (1953) pointed out that a tuberculous infection in contra distinction to other infections, rarely produce jaundice.

The mechanism of jaundice is not certain. Various factors have been mentioned by Prasad et al[16] (1973), like intrahepatic or extrahepatic obstruction and damage to liver parenchyma by granulomatous lesions or toxins. The incidence of jaundice is greater (24%) in cases of abdominal tuberculosis (Agarwal and Mehrotra[1], 1968).

SGPT: Study on SGPT shows a wide variation from 0-93%. Prasad et al[16] in a study of 116 cases could establish an abnormality only in 3.44%, while Munt (1972) in his study of 15 cases comes to the top with an abnormality of 93%. But Bowry[4] (1970) and Goldman[6] found no abnormality in their respective studies. The present series is in conjunction with Seharel and Smith (1969) and V.K. Jha et al[9] (1974) which showed abnormality of 10% each. Prasad et al[16] (1973) and Jha[9] (1974) pointed out that as radiological lesion increases, the chance of abnormality in SGPT is more. Here in our study also, all the 3 (11.11%) cases of abnormality were from far advanced group only.

SGOT: The present study records a lower percentage of abnormality with SGOT. Bowry[4] (1970) and Goldman[6] found 0% abnormality in their studies. Our study is in conformity with Prasad et al[16] (1973); both showing around 3% abnormality. However Favez (1964), Munt (1972) and

Jha[9] (1974) recorded little higher in their studies showing abnormality of 22%, 10% and 15% respectively. As in SGPT, here also Prasad[16] (1973) and Jha[9] (1974) found that more of abnormality in SGOT is in far advanced lesions. Present series also found the same with abnormality in far advanced and no abnormality in minimal and moderately advanced groups.

Serum Alkaline Phosphatase: On serum alkaline phosphatase, the present series correlates with most of the studies made by Bowry[4] (1970), Munt (1972) and Jha[9] (1974). Present study showed s.alkaline phosphatase abnormality of 26.67% while Bowry, Munt and Jha showed abnormality percentages of 16%, 34% and 21.6% respectively. Korn[10] (1959) shows the maximum abnormality with 40.9% while Bindra Ban[3] (1955) and Prasad et al[16] (1973) found no abnormality in any of the cases.

B.B. Maitra and C.R. Vyas[11] (1970) estimated serum alkaline phosphatase in 56 subjects in a controlled study. The patients were divided into normal subjects (11), tuberculous patients untreated (15), tuberculous patients treated (15) and resistant cases (15). Serum alkaline phosphatase was found to be raised significantly in tuberculous patients, possibly due to increased metabolic activity in response to caseation. As a result of anti-tubercular treatment, alkaline phosphatase level had a tendency to return towards normal in treated as well as resistant cases; though to a lesser extent in the latter group.

Serum Cholesterol: Regarding serum cholesterol; its value has been reported low by Eichelberger and Meehiskey, 1927 & Levison and Seigal, 1938. They have attributed lower resistance in pulmonary tuberculosis responsible for hypocholesterolaemia. The present series showed hypocholesterolaemia in 29.41% (Table No.11) which is in consistency with the findings of Yedurappa et al, 1966 (28%) and Prasad et al[16,] 1973 (35%). Low serum cholesterol was found in all types of radiological lesions. Kuldeep and Grewal[13] (1964), while studying serum cholesterol levels in cases of pulmonary tuberculosis of different categories have found low serum cholesterol values in all types of cases; the reduction being more marked in cases with active disease and under nutrition. The present series agrees with Kuldeep and Grewal[13] (1964). Prasad et al[16] (1973) found low serum cholesterol in acutely ill and far advanced cases as compared to moderately advanced and minimal lesions.

Hypocholesterolaemia may be due to multiple factors such as inadequate calories, altered cholesterol metabolism and diminished synthesis in liver. Mukherji[15] (1964); however has mentioned that pulmonary tuberculosis is not directly responsible for low serum cholesterol.

Total Serum Protein: The present series; showed abnormality (hypoproteinemia) percentage of 13.33%; which is on the lower side; and comes nearer to Bindra Ban[3] (1955) which showed 18% abnormality. Jha et al[9] (1974) found 0% hypoproteinemia i.e. total protein usually remains normal whereas Eichelberger and Mc Elusky (1927) said that total protein remains normal or above normal. Prasad et al[16] (1973) found higher incidence of hypoproteinemia (37%) with far advanced cases. In the present series also, hypoproteinemia was maximum in far advanced lesions.

Serum Albumin & Serum Globulin: The present series showed hypoalbuminaemia in 30% and hyperglobulinaemia in 20% (Table No. 13, 14). From the available literature, it is seen that both albumin and globulin are deranged in most of the studies. Going through other studies, S.Bowry[4] (1970) found abnormality percentages of 42% and 45%; whereas Jha[9] (1974) found 3.6% and 45% of that of s.albumin and s.globulin respectively.

The abnormality of s.albumin correlated with the severity of lesions as most of cases were belonging to far advanced group. Similar results were quoted by Eichelberger and Mc Elusky (1927), Pithew (1962), Mittal et al[12] (1965), Bowry et al[4] (1970), Prasad et al[16] (1973) and Jha et al[9] (1974). They are of the opinion that hypoalbuminaemia may be

due to dietary deficiency or by certain factors like chronic fever leading to catabolism, anorexia, albuminuria or massive chronic suppuration which may affect the metabolic activity of liver.

Jha et al[9] (1974) states that; though hyperglobulinaemia is expected in pulmonary tuberculosis; due to simultaneous hypoalbuminaemia, total serum protein remains normal. So in his study, even though he is getting slight hyperglobulinaemia in most of the cases and hypoalbuminaemia in some cases, total protein was normal in all cases.

In the present study, even though 9 cases (30%) showed hypoalbuminaemia and 6 cases (20%) showed hyperglobulinaemia, total protein was abnormal in only 4 cases (13.33%). Total protein was normal in all cases which showed hyperglobulinaemia. The 4 cases which showed hypoproteinemia were also showing hypoalbuminaemia. So, as stated by Jha[9] (1974), hyperglobulinaemia compensates for hypoalbuminaemia and keeps total protein normal in most cases.

A/G Ratio reversal: In the present series, abnormality in A/G ratio tops the list with 76.67% on comparison with other studies. In almost all the studies, A/G ratio recorded a higher change varying from 40% to 85%. The present series is in conformity with pioneers; Bindra Ban[3] (1955) and Sarin et al[18] (1957) which showed abnormality of 85% and 70% respectively. This much abnormality in A/G ratio can be expected as we expect hypoalbuminaemia and hyperglobulinaemia. Even slight change in both in a case can alter the A/G ratio. Prasad et al[16] (1973) and Mittal et al[12] (1965); each showed just 40% abnormality in A/G ratio.

Prothrombin time: Most studies are not available regarding the abnormal prolongation of prothrombin time. But prothrombin time is now considered as one among the liver function tests under clotting factors under clotting factors and so we included it in our series. Moreover this study was essential for the assessment of the patient before liver biopsy.

In the present series, 14 cases (46.67%) showed prolongation of prothrombin time. In one of our cases, there was an increase upto 40 seconds; 22 seconds more than control of 18 seconds; shows the potential value of prothrombin time. The only available literature regarding prothrombin time; studied by Sarin et al[18] (1957) showed abnormality in most of the cases.

Prolongation of prothrombin time may occur in severe hepatocellular necrosis as in hepatitis or cirrhosis. In our study out of 5 cases of parenchymal necrosis, 4 (80%) showed prolongation of prothrombin time.

L.F.T. changes: The studies on liver functions by various workers in pulmonary tuberculosis vary. The following table shows the L.F.T. changes (in percentage) as reported by different workers.

Table 23: L.F.T. changes (in percentage) as reported by different workers

L.F.T.	Bindra Ban 1955	Sarin et al 1957	Mittal 1965	Bowry et al 1970	Munt 1972	Prasad et al 1973	Jha et al 1974	Present series 2016
S.Bil	0	0	0	0	-	2.58	3.2	0
SGPT	-	-	-	0	93	3.44	10.8	10
SGOT	-	-	-	0	10	2.58	14.3	3.33
S.AlkP	0	0	-	16	34	0.00	21.6	26.67
S.Chol	75	52	-	0	-	35.34	-	29.41
Total s.prot	18	15	58	-	-	37.06	0	13.33
S.Alb	-	-	-	42	-	-	3.6	30
S.Glob	-	-	40	45	-	-	0	20
A/G ratio	85	70	-	-	-	40.51	-	76.67
Pro. time	-	49	-	-	-	-	-	46.67

Our study is not in full agreement with any of the studies. But all the liver functions show correlation with one worker or the other. In general, the present study is in line with Prasad et al[16] (1973).

L.F.T. & Radiological extent of disease: In far advanced group, all the functions except s. bilirubin showed abnormality from 3-78%; but in moderately advanced and minimal lesion groups, almost all the

functions were normal (Table No.18). As there were only 1 and 2 cases in minimal and moderately advanced groups, an intergroup comparison is not worth while with far advanced group with 27 cases.

Sarin et al[18] (1957) in the study of over 38 patients with far advanced lesions and 53 with moderate advanced lesions opinioned that the liver functions are a better guide to advancement of pulmonary lesions. V.K. Jha et al[9] (1974) stated that liver functions are indicators of severity of pulmonary tuberculosis. Prasad et al[16] is in agreement with Sarin et al[18] (1957) and Jha[9] (1974). The present series also is in accordance with Sarin et al[18] (1957), Jha[9] (1974) and Prasad[16] (1973).

Histological changes in Liver: A histopathology study of liver tissue obtained by needle biopsy showed specific and non-specific changes in liver (Table No.20). Specific changes like granuloma and tubercle formation gets a lower quantum while non-specific changes like cellular infiltration, Kupffer cell hyperplasia etc gets a major share in most of the studies.

The present study showed (Table No.21) that 21 out of 30 (70%) cases had non-specific changes only. Only one case (3.33%) showed specific changes by forming granuloma in liver tissue. The non-specific changes were cellular collections (26.67%), focal parenchymal necrosis (16.67%), Kupffer cell hyperplasia, R.E. cell hyperplasia and dilated sinusoids (26.67%), fibrotic and cirrhotic changes together (16.67%) and fatty infiltration (16.67%).

Infiltration with chronic inflammatory cell such as lymphocytes, plasma cells and neutrophils was present in most of the cases with cellular infiltration. The same findings were noted by Saphir (1957) and Bindra Ban (1955). Kupffer cell hyperplasia and R.E. cell hyperplasia were all noted by Bindra Ban (1955), Mukherjee et al[14] (1968) and Sankar and Prasanna[17] (1983).

Fatty infiltration in liver in chronic pulmonary tuberculosis was observed by Sarin et al[18] (1957), Bindra Ban[3] (1955), Mukherjee et al[14] (1968) and Sankar and Prasanna[17] (1983). Sarin explained that fatty infiltration may be due to anorexia, prolonged, malnutrition and disordered metabolism. The part played by anorexia is clearly disproved by Ban (1955), who compared pulmonary tuberculosis and non-tuberculous lesions affecting liver. He found that fatty infiltration was much more marked in tuberculous cases while anorexia in non-tuberculous cases.

Focal necrosis, fibrosis and cirrhosis to some workers like Bindra Ban[3] (1955) is a part of the same continuing process while Spring and Saphir do not believe that classical cirrhosis can result from pulmonary tuberculosis. The correlation between pulmonary tuberculosis and cirrhosis of liver is one of the controversial issues. Periportal fibrosis has been noted by Mukherjee[14] (1968), Sankar and Prasanna[17] (1983) and Prasad et al[16] (1973).

Table 24: Frequency of Histological changes (in percentage) as reported by different workers

Histological changes	Present Series 2016	Sarin et al 1957	Bindra Ban 1955	Bowry 1970	Prasad et al 1973	Prasanna and Sankar 1983
Definite tubercle	3.33	15	9	25	-	8
Focal cellular collections	26.67	35	33	9	26.8	21
Focal necrosis	16.67	47	12	16	34.78	1
Fatty infiltration	16.67	27	35	44	13.04	21
Fibrotic changes	16.67	27	39	12	21.73	2
R.E. cell hyperplasia	26.67	57	6	-	13.04	23
Total no. of cases	**30**	**100**	**34**	**32**	**23**	**100**

The above table shows various findings obtained by various workers in histopathology of liver in pulmonary tuberculosis. The present series doesn't correspond to any of the single study; but most of the findings correlate with many workers.

The incidence of non-specific lesions is quite high in the present study and it may be due to associated nutritional and toxic factors. The lesions may appear as a reaction to the tissue breakdown products and toxins elaborated by tuberculous infection. Ban (1955), Buckingham[5] (1956) and Prasanna[17] (1983) have suggested that non-specific lesions in liver biopsy appear to represent a reaction to endogenous toxins elaborated by tubercle bacilli.

As pointed out by various workers, the non-specific changes can be due to associated nutritional factors, some

unknown disease, tuberculous drugs or tuberculosis itself. In the present study also, these possibilities cannot be excluded as the study included both fresh cases and cases undergoing treatment. That may be the reason why 21 out of 30 cases (70%) showed non-specific changes.

Though the liver is invaded by tuberculous bacilli by haematogenous route (Sarin et al[18], 1957; Prasanna and Sankar[17], 1985) in all patients with pulmonary tuberculosis, specific changes is noted only in one case which demonstrated a granuloma. None of the specimens showed the presence of tubercle bacilli. The incidence of hepatic granuloma in studies reported by other workers is given below.

Table 25: Incidence of hepatic granuloma

Author/Reference	No. of cases studied	Percentage
Bindra Ban (1955)	59	20
Prasad et al (1973)	23	0
Sarin et al (1957)	100	15
Sen and Chaudhary (1966)	60	3.3
Mukerjee et al (1968)	38	10.5
Sobti and Hoon (1977)	62	15
Prasanna and Sankar (1983)	100	8
Present series (2016)	30	3.3

Our study recorded a lower percentage when compared with most of other workers. However, present study correlates with Sen and Chaudhary[19].

The infrequency of hepatic granuloma and absence of AFB in the lesions in present study suggests that the liver does not offer a favorable environment for the growth of tubercle bacilli. The lone case of granuloma (3.3%) belonged to far advanced pulmonary tuberculosis. Though the patient who demonstrated granuloma exhibited liver enlargement, there were many other patients who had liver enlargement but failed to show granulomas and showed only specific changes. Thus the enlargement of liver in presence of pulmonary tuberculosis does not indicate conclusively about presence of granuloma. The same observation was made by Prasanna[17] (1983) also.

As noted from Table no.25, hepatic granuloma has been found from 0-20%. Bindra Ban[3] records the highest with 20%. However Prasad et al[16] (1973) failed to demonstrate any granuloma in his study. According to him, the increased incidence of granuloma noted by some workers may be due to inclusion of patients with extensive diseases, miliary tuberculosis, tuberculous lymphadenitis and abdominal tuberculosis or due to meticulous search for tuberculous involvement in the liver biopsy specimen. We also did not include abdominal and glandular tuberculosis and failed to get a miliary tuberculosis case.

Roentgenographic features with Histopathology: Sarin et al[18] (1957) and Prasanna and Sankar[17] (1983) showed that advancement of pulmonary lesion is significantly correlated with the extent of hepatic parenchymal involvement. In our study also, we found more changes with far advanced lesions. However it is not possible in our study how far the parenchymal involvement in various radiological lesions is as there are only one and two cases in minimal and moderately advanced group respectively.

L.F.T. and Histopathology: In our study, out of 8 normal liver tissues by HPE, 3 patients did not show any change in any of the L.F.T. The next 5 showed changes in only one or two L.F.T. But in all the liver tissue which showed definite specific and non-specific changes, L.F.T. was involved in at least one or two function. This clearly shows that at least there is some significant relationship between deranged histopathology and liver functions. The same is seen by Bindra Ban[3] (1955) and Sarin et al[18] (1957). However no definite correlation was observed between histopathology and deranged liver functions by Seife et al (1957), Bowry et al[4] (1970) and Prasad at al[16] (1973).

CONCLUSIONS

This study and previous studies show a remarkable finding and that is disagreeable among various function tests. This may be due to:

- All studies were carried out at different periods ranging from 1955-2016. During this period, there has been considerable change in socioeconomic status and nutritional standards of people in India.
- Different workers have studied in different geographical location within and outside India where personal habits,

nutritional standards and economic status differ.

- Different workers have selected different groups of patients with specific purposes either of carrying out liver biopsy or enzymatic studies or studies of other L.F.T.
- Different age groups and different radiological extent of diseases were found in different studies.

Thus the results of anyone study in no way can be compatible to another study. However, certain very clear findings are helpful in giving some conclusions; one of which is that granuloma formation is comparatively a rare phenomena and liver biopsy can hardly be useful as a routine procedure to rule out tuberculosis in doubtful cases of systemic tuberculous infections.

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