

Serum Transaminase Activity in Leprosy in Relation to Liver Damage

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The study of transaminase activity in human serum has opened a large field of clinical research. The enzyme transaminase is widely distributed in animal tissues and has been shown to be increased in its concentration during certain diseases. Serum transaminase assays in particular have been widely used as an aid to diagnosis for the last 10 years. Attention has been drawn lately toward two types of serum transaminase: (1) glutamic oxalo-acetic transaminase (SGO-T), and (2) glutamic pyruvic transaminase (SGP-T). Serum transaminases SGO-T and SGP-T are concentrated mainly in heart muscle and liver, but are found also in skeletal muscle, pancreas, kidney and brain. Thus serum transaminase levels are raised in various clinical conditions involving damage to heart muscle⁽¹⁰⁾, in various types of hepatic disorders⁽¹⁶⁾, and in various myopathies⁽¹¹⁾.

No information is available regarding activity of serum transaminase in leprosy. The study of this enzyme in leprosy is of clinical and pathologic interest for many reasons. Leprosy is characterized by granulomatous lesions chiefly affecting skin, organs of the reticuloendothelial system, skeletal muscle and nerves. Involvement of the liver by miliary lepromas in lepromatous leprosy is common. Secondary changes characterized by cirrhosis and fatty change are also observed in leprosy patients. As liver is a rich source of serum transaminase, especially SGP-T, it would be interesting to determine its levels in different types of leprosy and to correlate it with histologic changes observed in the liver.

Work now under way deals with the evaluation of transaminases SGO-T and SGP-T in all types of leprosy and correlation of their concentration with routine liver function tests and histologic changes in liver.

MATERIALS AND METHODS

The cases for this study were selected from the leprosy ward attached to the Medical College Hospital in Nagpur. The patients were admitted during the period August 1962 to August 1963. All were well established cases of leprosy, with at least one to two years of clinical history. They were admitted either for lepra reaction or for surgical procedures in the treatment of trophic ulcers and gangrene. A total of 72 cases were studied during this period. All or most of the cases were subjected to laboratory investigations as follows:

(1) Skin clipping for acid-fast bacilli and skin biopsy to determine the type of leprosy histologically⁽⁷⁾.

(2) Liver function tests^(9, 13, 18, 23).

(3) Liver biopsy by Vim Silverman's method⁽¹⁹⁾. Successful biopsy was available in 58 cases. Routine hematoxylin and eosin and Fite-Faraco stains for acid-fast bacilli were made in each case⁽⁷⁾.

(4) SGO-T and SGP-T determinations by the Mohun and Cook method⁽¹⁵⁾.

(5) Muscle biopsy in 56 cases from sites of gross muscular wasting. The findings will be discussed elsewhere.

After thorough clinical examination and histopathologic examination of a skin piece in every case, cases were grouped as (a) lepromatous, (b) tuberculoid, or (c) indeterminate.

The criteria followed for clinical and histopathologic differentiation were those set forth by Cochrane⁽³⁾.

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OBSERVATIONS

Histologic changes in liver in different types of leprosy. Histologic changes noted in 58 liver biopsies in the present study are discussed below. These were made up of 43 lepromatous, 10 tuberculoid and 5 indeterminate type cases.

Of 43 lepromatous cases, 8 presented a completely normal picture. Fifteen showed

histologic changes characterized by lymphocytic and histiocytic cellular aggregations, mainly around portal areas (Fig. 1). Some showed a definite increase in fibrous tissue chiefly around portal areas, together with cellular infiltrations and hyperplasia of the Kupffer cells. Liver cells showed vacuolar degeneration with multiplication of nuclei (Fig. 1). Five cases showed a definite increase in fibrous tissue, with dis-

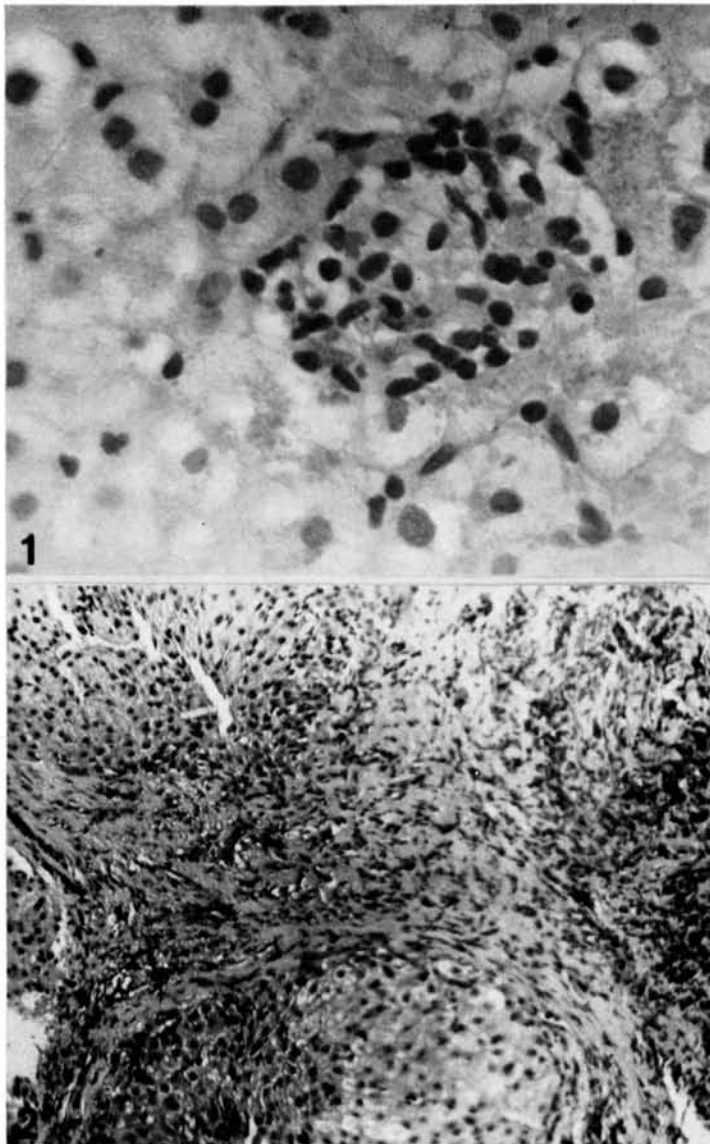


FIG. 1. Photomicrograph of liver showing focal collection of inflammatory cells, mainly lymphocytes. Liver cells show vacuolar degeneration with multiplication of nuclei. (High power)

FIG. 2. Photomicrograph of liver showing portal cirrhosis, a common histologic finding in leprosy. (Low power)

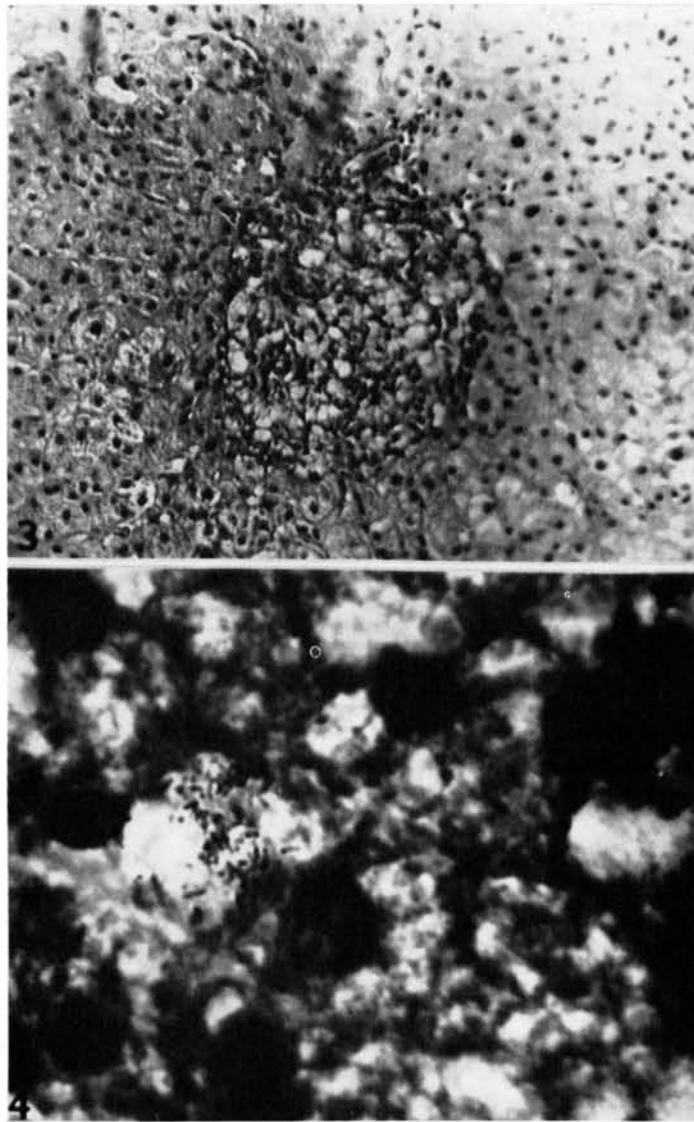


FIG. 3. Photomicrograph of liver showing a miliary leproma consisting of vacuolated Virchow cells, histiocytes and monocytes. It is limited by a thin band of connective tissue. (Low power)

FIG. 4. Photomicrograph of liver showing presence of leprosy bacilli in vacuolated Virchow cells. (Oil immersion)

tortion of the hepatic architecture and fatty change, resembling portal cirrhosis (Fig. 2). All of these cases were negative for acid-fast bacilli. Fifteen cases showed specific changes of leprosy characterized by the formation of miliary lepromas. These consisted of vacuolated Virchow cells. The latter were seen usually at the peripheries of the hepatic lobules, grouped around necrosed hepatic cells, and surrounded by

thin bands of connective tissue (Fig. 3). Acid-fast stains by the Fite-Faraco method for lepra bacilli were positive in nine cases. The bacilli were found chiefly in the foamy cells of Virchow, in the intercellular spaces, and in Kupffer cells, grouped as globi (Fig. 4).

Of 10 tuberculoid cases, one presented a histologically normal picture. Five cases showed varying degrees of atrophy of liver

cells, with focal collections of inflammatory cells, mainly lymphocytes and monocytes, but no giant cells or definite tubercle formation. Two cases showed increase in periportal fibrous tissue, with aggregation of focal inflammatory cells in these areas. Two cases showed distinct cirrhosis with fatty infiltration. Leprosy bacilli were not detected in any of these cases.

Of five indeterminate cases, three presented a normal picture. One showed a definite miliary leproma of the type described above and was positive for lepra bacilli. The remaining case showed cirrhotic changes.

Liver function tests in leprosy. The following liver function tests were made routinely in all the cases: (a) total protein⁽²¹⁾, (b) serum albumin⁽²¹⁾, (c) serum globulin by subtracting serum albumin from total proteins, (d) serum alkaline phosphatase⁽⁹⁾, (e) serum cholesterol⁽¹⁸⁾, and (f) thymol turbidity⁽¹³⁾.

The results of liver function tests in relation to different types of leprosy are summarized in Table 1. The relations of histologic changes in the liver and transaminase activity are shown for different types of leprosy in Tables 2, 3 and 4.

DISCUSSION

Histologic alterations in the liver in different types of leprosy have been investigated by many workers in the past. Bru and Rollier⁽¹⁾, studied histologic changes in the liver in 38 cases, 32 of which were lepromatous, five tuberculoid and one indeterminate. They found manifest lesions in all the specimens, mainly in the mesenchymal elements. All cases indicated a hematogenous origin of the bacilli, which were found in 33 of the specimens, including two from tuberculoid cases.

Camain *et al.*⁽²⁾ made liver biopsies in 41 tuberculoid and 37 lepromatous cases. Of the 41 tuberculoid cases 13 showed alterations. These consisted variously of groups of lymphocytes and histiocytes in portal areas or in lobules, which later developed into tubercles and subsequently underwent fibrosis. Bacilli were extremely rare. Of the 37 lepromatous cases 35 presented microscopic groups of vacuolated

Virchow cells. In three cases of indeterminate type no specific changes were seen.

Fazio *et al.*⁽⁶⁾ studied histologic findings in the liver in four lepromatous cases, and found changes varying from mere lymphocytic infiltration to active granuloma formation with foamy cells in all four. Treatment caused no histologic alterations in their cases.

Histologic alterations in the liver in tuberculoid and indeterminate types of leprosy in the investigation here reported compare closely with those reported by the previous authors. Liver changes specific for lepromatous leprosy were found in only 15 out of 43 cases, i.e., about 40 per cent of cases, in contrast to about 90 per cent as noted by Camain *et al.*⁽²⁾. All the lepromatous cases studied here had undergone long courses of treatment by diaminodiphenyl sulfone. This may account for the failure to find active lepromatous lesions in most of the cases in the present study.

It might be expected that important histologic changes could be correlated with altered liver function tests, which have received wide attention by various workers. Verghese and Job⁽²¹⁾ studied the histopathology of the liver and liver function in 19 cases of different types of leprosy. They found diminished liver function in three lepromatous, two borderline and one tuberculoid patient, but the altered liver function could not be correlated with the presence of leprotic granulomas in the liver. Tarabini⁽¹⁹⁾ reported hyperproteinemia in lepromatous type leprosy. He attributed this principally to hyperglobulinemia. He also reported lowering of cholesterol levels in 52 lepromatous cases. Kusaka⁽⁸⁾ also reported lowered serum cholesterol values in lepromatous leprosy. Lundin and Ross⁽¹²⁾ reported reversal of the albumin-globulin ratio and considerable increase in globulin in reactional stages of leprosy. Ramu and Nagrajan⁽¹⁷⁾ reported lowered serum cholesterol and normal alkaline phosphatase in 25 cases of lepromatous leprosy both during and after reaction. Dhople and Magar⁽⁵⁾ reported an increase in average proteins and a reversal of the albumin-globulin ratio in lepromatous leprosy.

In the series here reported the highest average of serum proteins (7.4 gm.%), was

found in lepromatous leprosy (Table 1). This compares closely with Dhople and Magar's average value of 7.7 gm. per cent. In the present series the albumin-globulin ratio was found to be reversed in lepromatous leprosy, but not in tuberculoid and indeterminate types. These results also agree well with those of Dhople and Magar.

The average value for serum cholesterol in lepromatous leprosy was 125 mgm. per cent (Table 1). This compares closely with the average value found by Ramu and Nagrajan (126 mgm.%). It is well below the normal limits.

Serum alkaline phosphatase and thymol turbidity showed average values well within normal limits. All cases with raised transaminase activity and hepatic involvement showed normal serum alkaline phosphatase and thymol turbidity values, indicating that transaminase estimation can prove a more sensitive index of liver damage in leprosy than these routine liver function tests.

Liver is the richest source of transaminase next to cardiac muscle. In liver diseases large quantities of transaminase enter the blood (4, 14, 16, 22). Acute hepatitis is distinguished from other liver diseases in that the GP-T rise is more than that of GO-T (4). Wroblewski (22) stated that hepatic cirrhosis causes moderate increase in both transaminases. The value is higher in the decompensated than in the compensated form of cirrhosis. Thus it is of interest to correlate serum transaminase levels in leprosy with histologic alterations in the liver. The histologic changes, which have been described in detail, proved not to be associated with any derangement in routine liver function tests, as has been pointed out.

Of the eight lepromatous cases showing normal histology only one showed a high transaminase level (Table 2). This was a frank lepromatous case with skin showing lepra bacilli. A muscle biopsy in this case showed destruction of muscle fibers with replacement fibrosis and collections of inflammatory cells between the fibers, as noted elsewhere. The increased transaminase activity in this case can be attributed

TABLE 1. Liver function tests in different types of leprosy. Averages of 72 cases.

Type of leprosy	Av. total protein gm. %	Av. albumin gm. %	Av. globulin gm. %	Alk. phosphate K.A. units	Serum cholesterol mgm. %	Thymol turbidity units	SGO-T av. value Cabaud units	SGP-T av. value Cabaud units
Lepromatous	7.4	3.6	3.8	5.8	125	2.4	27.5	39.5
Tuberculoid	6.7	3.4	3.3	6.3	158	2.7	24.5	24.3
Indeterminate	6.8	3.5	3.3	5.4	154	2.6	11.1	25.1

TABLE 2. Relation between serum transaminase activity and histologic changes in liver in lepromatous leprosy.

Histologic changes in liver	No. of cases	No. cases positive AFB	No. showing increased transaminase activity	SGO-T		SGP-T	
				(Cabaud units)		(Cabaud units)	
				Range*	Average*	Range*	Average*
Normal	8	0	1	60	—	50	—
Increased periportal fibrosis with focal inflam.	10	0	6	3-47	27.8	20-84	59.3
Nutritional deficiency changes with focal inflam.	5	0	0	—	—	—	—
Cirrhosis with fatty change	5	0	5	10-51	29.5	39.89	62
Miliary leproma	12	7	10	6-43	25.6	44-80	61.6
Miliary leproma with cirrhosis	3	2	3	13-63	37.7	47-116	81

*Of cases showing raised transaminase activity either SGO-T or SGP-T.

TABLE 3. Relation between serum transaminase activity and histologic changes in the liver in tuberculoid leprosy.

Histologic changes in liver	No. cases cases	No. cases positive AFB	No. showing increased transaminase activity	SGO-T		SGP-T	
				(Cabaud units)		(Cabaud units)	
				Range*	Average*	Range*	Average*
Normal	1	0	0	—	—	—	—
Increased periportal fibrosis with focal inflam.	2	0	0	—	—	—	—
Nutritional atrophy	5	0	0	—	—	—	—
Cirrhosis with fatty change	2	0	1	45	—	45	—

*Of cases showing raised transaminase activity either SGO-T or SGP-T.

to these muscle changes, as muscle is also a rich source of transaminases.

Of the five cases showing varying degrees of atrophy of liver cells, with distinct signs of inflammation, none showed increase in transaminase values.

Of the 10 cases showing periportal increase in fibrous tissue, six showed definite increase in transaminase activity. The mean value was 27.8 Cabaud units in the case of SGO-T and 59.3 units in that of SGP-T. Although the mean value of SGO-T is well

TABLE 4. Relation between serum transaminase activity and histologic changes in the liver in indeterminate leprosy.

Histologic changes in liver	No. cases	No. cases positive AFB	No. showing increased transaminase activity	SGO-T		SGP-T	
				(Cabaud units)		(Cabaud units)	
				Range*	Average*	Range*	Average*
Normal	3	0	0	—	—	—	—
Cirrhosis	1	0	1	8	—	43	—
Miliary leproma	1	0	0	—	—	—	—

*Of cases showing raised transaminase activity either SGO-T or SGP-T.

within the upper limit of normal, it is about one and a half times the mean value calculated for normal controls (19 Cabaud units). The mean value of SGP-T was 59.3 Cabaud units, well above the normal limit, but it can only be called borderline.

All five cases with cirrhosis and fatty change showed high transaminase values, with mean values of 29.5 Cabaud units for SGO-T and 62 for SGP-T. Both of these mean levels are higher than the levels in previous cases showing only periportal fibrosis, a fact indicating that the cirrhotic process found in leprosy may be the result of a subacute form of hepatitis caused by leprosy bacilli.

Of 15 cases showing definite miliary leproma formation, 13 showed definite increase in transaminase activity. The mean of SGO-T was 25.6 Cabaud units and that of SGP-T 61.6 units, i.e., three times the average value of 20.5 Cabaud units in normal controls. All three cases showing miliary leproma with cirrhosis showed higher transaminase activity. The mean values in these cases exceeded those of all the previous cases.

Tuberculoid and indeterminate types of leprosy presented an entirely different picture (Tables 3 and 4). Only one of the two tuberculoid cases with definite cirrhotic changes showed an increase in transaminase levels. The same was true of the case with indeterminate type of leprosy. Only one case showing cirrhotic change showed high transaminase levels.

Acute hepatitis is known to cause more rise in SGP-T than in SGO-T⁽⁴⁾. Cirrho-

sis, on the other hand, causes a moderate rise in both transaminases⁽²²⁾. In the present series, in the cases showing high transaminase activity, the average SGP-T rise has been observed to be three times greater than the average SGO-T values. This high SGP-T activity suggests parenchymal damage to the liver in lepromatous leprosy.

Thus cirrhotic changes, which are found commonly in lepromatous leprosy, may be the result of liver cell damage caused by leprosy bacilli, or their products, or impaired nutrition.

SUMMARY

Fifty-eight liver biopsies were obtained from different types of leprosy. Normal histology was observed in 12 cases, eight lepromatous, three tuberculoid, and one indeterminate. All showed normal transaminase activity. Periportal fibrosis, nutritional atrophy and focal inflammation were observed in 22 cases (15 lepromatous, 7 tuberculoid). Of these, six cases (all lepromatous) showed increased transaminase activity. Cirrhosis was observed in eight cases, (5 lepromatous, 2 tuberculoid, and 1 indeterminate). Of these, five cases (all lepromatous) showed increased transaminase activity. Miliary leproma was detected in 16 cases (15 lepromatous, 1 indeterminate), and 13 of these showed increased transaminase activity. Liver function tests were within normal limits in all the cases.

These observations suggest that the relative rise in SGP-T seen in lepromatous

leprosy, indicates a toxic effect of leprosy bacilli on the hepatic cells. Our observations also point out that a rise in SGP-T is a more sensitive index of hepatic involvement in leprosy, than the routine liver function tests.

RESUMEN

Cincuenta y ocho biopsias del hígado se obtuvieron de diferentes tipos de lepra. Histología normal fue observada en 12 casos (8 lepromatosos, 3 tuberculoides, y 1 indeterminado). Todos mostraron normal actividad transaminasa. Fibrosis periportal, atrofia nutricional e inflamación focal fueron observados en 22 casos, (15 lepromatosos, 7 tuberculoides). De estos, 6 casos (todos lepromatosos) mostraron aumento de la actividad transaminasa. Cirrosis se observó en 8 casos, (5 lepromatosos, 2 tuberculoides, y 1 indeterminado). De estos, 5 casos (todos lepromatosos) mostraron aumento de la actividad transaminasa. Lepromas miliares se encontraron en 16 casos (15 lepromatosos, 1 indeterminado), y 13 de estos mostraron aumento de la actividad transaminasa. Prueba de la función hepática fue en los límites normales en todos los casos.

Estas observaciones sugieren que el relativo aumento en SGP-T observado en lepra lepromatosa, indica un efecto tóxico de los bacilos en las células hepáticas. Nuestras observaciones señalan también que un aumento en SGP-T es un índice más sensible de comprometimiento hepático en lepra que las pruebas rutinarias de la función hepática.

RÉSUMÉ

Cinquante huit biopsies du foie ont été rassemblées, prélevées chez des malades atteints de différents types de lèpre. Dans 12 cas, 8 lepromateux, 3 tuberculoides et 1 indéterminé, on a observé une histologie normale. Toutes les biopsies ont témoigné d'une activité normale en transaminase. Dans 22 cas (15 lepromateux et 7 tuberculoides), on a relevé de la fibrose péri-portale, de l'atrophie nutritionnelle et de l'inflammation focale. Parmi ces cas, 6 (tous lepromateux) montraient une augmentation de l'activité en transaminase. De la cirrhose a été notée dans huit cas (5 lepromateux, 2 tuberculoides et un indéterminé). Parmi ceux-ci, 5 (tous lepromateux) témoignaient d'une activité accrue en transaminase. Des lépromes miliaires ont été détectés dans 16 cas (15 lepromateux, 1 indéterminé); 13 de ceux-

ci montraient une augmentation de l'activité en transaminase. Les épreuves de la fonction hépatique ont été dans les limites normales dans tous les cas.

Ces observations suggèrent que l'augmentation relative dans le SGP-T constatée dans le lepromateux témoigne d'une action toxique des bacilles de la lèpre sur les cellules hépatiques. Nos observations soulignent aussi qu'une augmentation dans le SGP-T est un indice plus sensible que les épreuves habituelles de la fonction hépatique en ce qui concerne l'atteinte du foie dans la lèpre.

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