A Histopathologic Study of Striated Muscle Biopsies in Leprosy¹

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Changes in muscles in leprosy have been described by Ishihara (3), Convit et al (1) and Job et al (4). Job et al studied histopathologic changes in six striated muscle and two nonstriated muscle (dartos muscle) biopsies. Two of the cases were also studied by electron microscopy. They described perivascular granulomas, extending on the muscle fibers associated with their subsequent degeneration and fibrosis. Acid-fast bacilli were also seen inside macrophages and muscle cells in some cases. The present study describes the histopathologic changes seen in striated muscle biopsies from normal appearing biceps muscles which did not show any evidence of atrophy or functional impairment in 50 cases of leprosy.

MATERIALS AND METHODS

Leprosy cases. Fifty cases of leprosy, 40 lepromatous (LL) and 10 nonlepromatous (NL) have been studied during the past year. The cases were diagnosed and typed clinicobacteriologically and the classifications confirmed histopathologically by skin biopsies. Forty-one patients were male and nine were female. Their ages ranged from 15 to 65 years.

Muscle biopsy. Muscle biopsies were obtained in all 50 cases from normal appearing biceps muscles which did not show any clinical evidence of atrophy or functional impairment. They were taken from the midportion of the muscle where more muscle spindles were expected. Approximately $3 \times 1 \times 1$ cm muscle tissue was obtained in each instance and was divided into two parts, one to be sectioned transversely and the other longitudinally. Both of the pieces were processed, paraffin sections cut, and stained by the following technics employing standard procedures: hematoxylin and eosin, Masson's trichrome, Mallory's phosphotungstic acid hematoxylin, Gomori's silver impregnation for reticulin fibers, and Ziehl-Neelsen's stain for acid-fast bacilli. The sections were examined with respect to: granuloma formation, their constituent cells, size, location and presence of acid-fast bacilli; changes in muscle fibers as loss of striations, hyaline change, fatty change, necrosis and fibrosis; changes in epimysium, perimysium and endomysium; changes in nerve fibers.

OBSERVATIONS

All cases under study were divided into two major groups: lepromatous leprosy (40 cases) and nonlepromatous leprosy (10 cases). The histopathologic changes noted in the muscles are recorded in Tables 1, 2 and 3. Changes in muscle fibers consisted of granuloma or leproma formation, loss of striations, hyaline change, fatty change, sarcolemmal change along with endomysial thickening, necrosis and fibrosis, alone or in combination with each other.

Inflammatory nodule (granuloma or leproma) formation was noted in 34% of all cases, being slightly more frequent in the LL type (35%) than in the NL type (30%). One or more than one nodule, in different locations, were seen in the same section. Loss of cross striations and hyaline change were observed in 52% of the total cases, 50% of cases being of the LL type and 60% of the cases of the NL type. Twenty percent of all cases showed fatty change, 17.5% being LL type and 30% being NL. Sarcolemmal changes along with endomysial thickening were seen in 20% of all cases, being more frequent in LL (22.5%) than in NL (10%). Twenty-six percent of the cases (25% of the LL type and 20% of NL type) showed necrosis of muscle fibers. Fibrosis was observed in 24% of all cases; in 25% and 20% of LL and NL types respectively. The leprous nodules were distributed in different locations in the muscle with respect to muscle fibers or in relation to blood vessels and nerves. More than one lo-

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Pattern of change	Tota 50 c	al of ases	Tota cases	1 LL (40)	Total NLL cases (10)		
	No.	%	No.	%	No.	%	
Granuloma	17	34	14	35	3	30	
Loss of striations	26	52	20	50	6	60	
Hyaline change	26	52	20	50	6	60	
Fatty change	10	20	7	17.5	3	30	
Sarcolemmal change	10	20	. 9	22.5	1	10	
Necrosis	13	26	10	25	2	20	
Fibrosis	12	24	10	25	2	20	

TABLE 1. Incidence of pathologic changes in muscles in leprosy.

LL = lepromatous leprosy; NLL = nonlepromatous leprosy.

TABLE 2. Details of granulomas.									
	Total ca granulo								
Granulomas	No.	%	LL	NLL					
A. Location									
Perivascular	4	23.5	4						
In-between muscle fibers	3	17.6	2	1					
In muscle fibers	5	29.4	5	-					
Perineural	2	11.7	2						
Confluent	5	29.4	3	2					
B. Size									
Focal and small	11	64.7	10	1					
Large and extensive	5	29.4	3	2					
C. Structure									
Predominantly foam cell type	9	53	9						
Predominantly other cell type	8	47	5	3					
D. Acid-Fast Bacilli									
Solidly stained bacilli	3	17.6	3						
Acid-fast granular material	11	64.7	11	_					

LL = lepromatous; NLL = nonlepromatous.

cation was seen in some cases. The locations were: perivascular, in-between muscle fibers (intermysial), in the muscle fibers (intramysial), perineural, and confluent.

A perivascular nodule was defined as focal, small, and situated around or beside blood vessels closely applied to them. Twenty-three and a half percent of all nodules were perivascular and were noted only in LL cases. The intermysial granulomas were localized between muscle fibers, separating them without encroaching upon or destroying them and in the midst of which a blood vessel could not be identified. They were also focal and small and constituted 17.6% of all the nodules. Intramysial nodules (29.4%) were seen inside the sarcolemmal sheaths, extending along their sarcoplasm and partially replacing the muscle fiber; perineural nodules, seen in two cases (11.7%), were focal, small, and situated adjacent to an intramuscular nerve which itself was not involved in the process. Large nodules, the localization of which could not be delineated because of their greater dimensions and extensive destruction of the muscle fibers, were called confluent granulomas and were seen in 29.4% of the cases. The latter were noted in 6 of 17 cases (29.4%).

Structure of granulomas. Mainly two types of nodules were noted. One was a leproma with foam cells predominating and the

Pattern of change	Up to 20 years		21 to 40 years			41 to 60 years			61 years and above			
	Total 6 cases	LL (5)	NLL (1)	Total 30 cases	LL (26)	NLL (4)	Total 12 cases	LL (9)	NLL (3)	Total 2 cases	LL (1)	NLL (1)
Granuloma	3 50%	3 60%		10 33.3%	7 23.9%	3 75%	4 33.3%	4 44.4%		_	_	
Loss of striations	2 33.3%	2 40%		14 46.6%	10 38.46%	4 100%	9 75%	7 77.7%	2 66.66%	1 50%	1 100%	_
Hyaline change	2 33.3%	2 40%		14 46.6%	10 38.46%	4 100%	9 75%	7 77.7%	2 66.66%	1 50%	1 100%	
Fatty change	2 33.3%	2 40%	-	3 10%	2 7.69%	1 25%	4 33.3%	3 33.3%	1 33.3%	- 1 50%	_	1 100%
Sarcolemmal change	=	_		6 20%	5 19.23%	1 25%	3 25%	3 33.3%		1 50%	1 100%	_
Necrosis	3 50%	3 60%	_	7 23.3%	4 15.38%	3 75%.	3 25%	3 33.3%		-	= 1	
Fibrosis	1 16.6%	1 20%		8 26.6%	6 23.07%	2 50%	3 25%	3 33.3%			-	

 TABLE 3. Incidence of pathologic changes in muscles in different age groups of leprosy patients.

LL = lepromatous; NLL = nonlepromatous.

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FIG. 1. Intramysial granulomas extending along sarcoplasm. H & E stain. ×450.



FIG. 2. Well-formed intramysial granuloma which has completely destroyed the muscle fiber. H & E stain. ×300.

other approximated a granuloma with macrophages and lymphocytes predominating. The former constituted 53% of all cases of nodules and were seen only in LL. The latter constituted 17% of all cases of nodules and were observed both in LL and NL. Though there were other inflammatory cells also in the lepromas, they were insignificant in number in comparison to foam cells; peripheral portions of these granulomas were speckled with lymphocytes and plasma cells. In a few instances lymphocytes and plasma cells were seen sparsely admixed with the foam cells. Polymorphonuclear leucocytes could not be identified in these lesions. The granulomas showed mainly tissue histiocytes, lymphocytes and plasma cells, though there were a few foam cells also. These cells were seen in closely packed sheets in biopsies obtained from NL cases. In these granulomas there was more free admixture of all the above-mentioned inflammatory cells as compared with the lepromas. Three cases of NL showed granulomas without foam cells. In addition, areas of necrosis and Langhan's giant cells were present. In one of these cases a well-circumscribed focal granuloma was seen in-between muscle fibers, which was made up of histiocytes, lymphocytes, a few plasma cells and Langhan's type giant cells.

Apart from these two types of well formed nodules, focal collections of inflammatory cells without definite granuloma formation were observed in biopsies obtained from cases of LL (3 cases, not included in the table). These focal collections were present inbetween muscle fibers, and consisted of lymphocytes and scanty plasma cells. Polymorphonuclear leucocytes could not be identified in these foci.

Acid-fast bacilli. Solidly-stained leprosy bacilli could be detected in 17.3% of all cases which showed lepromas, while acid-fast granular material was noted in 64.7% of all cases with lepromas. None of the cases of NL type, either with granulomas or without granulomas, showed any acid-fast bacilli or granular matter.

Loss of striation, hyaline change and fatty change. Loss of striation and hyalinization of muscle fibers were observed in a larger number of cases (52%) as compared to other changes being seen in 50% of LL and 60% of NL types. They were present in muscle fibers



FIG. 3. Extensive foam cell leproma. H & E stain. ×300.



FIG. 5. Extensive fatty change in muscle (LL). H & E stain. $\times 100$.



FIG. 4. A well-formed tuberculoid granuloma from NL. H & E stain. ×450.

in the neighborhood of nodular lesions as well as away from them. Many of the muscle fibers showing nodular inflammation had intact cross striations even up to the point of encroaching granulomatous reaction. Only ten cases (20%) showed fatty change; seven cases (17.5%) being LL and three (30%) of NL type.

Sarcolemmal changes. Thickening of endomysial sheaths was observed in ten cases (20%), of which nine (22.5%) were LL type and one case (10%) NL. This change was well brought out by staining the sections with Gomori's silver impregnation technic. Some of the muscle fibers in a few cases also showed increased number of sarcolemmal nuclei which were centrally placed in the cytoplasm.

Necrosis. In general, where the nodules were large, confluent and pressing on muscle fibers, there was necrosis of the latter. Where nodules were smaller and less pressing on the fibers, necrosis was less and even absent. This was irrespective of case type, with necrosis appearing in 13 instances (26%).

Fibrosis. Fibrosis in and around nodules was seen in 12 cases (24%), 10 cases (25%) being LL type and 2 cases (20%) being NL.

In all these cases fibrosis was minimal to moderate. Extensive fibrous replacement of muscle fibers was not seen in any case. Apart from this, some cases showed thickening of endomysium as described above and even broad bands of loose connective tissue separating the muscle bundles. Sections from other cases showed focal areas of fibrosis interrupting the muscle fibers without the presence of active nodules in their vicinities.

Incidence of pathologic changes in different age groups. The cases studied were divided into four age groups (Table 3) as follows: Group I, up to 20 years of age; Group II, 21 to 40 years; Group III, 41 to 60 years; and Group IV, 61 years and above.

Granulomas and necrosis show a much higher incidence in the relatively young patients up to the age of 40, than in the older patients. Other changes did not show a significant difference in incidence in different age groups, although they were seen slightly more often in older patients. All the lesions were noted more frequently in males than in females. However, the small number of females in this study makes the significance of this observation questionable.

Incidence of combined pathologic changes. In the majority of cases, different pathologic changes were observed in different combinations. Only granulomas unassociated with any other change were observed in two cases (4%), both being cases of LL type. Granulomas associated with other degenerative changes, excluding endomysial thickening, were noted in 15 cases (30%), of which 12 cases (30%) were of LL type and 3 cases (30%) were of NL type. Granulomas associated with other degenerative changes, including endomysial thickening, were seen in 13 cases (26%); 12 cases (30%) being LL and 1 case (10%) NL. Degenerative changes exclusive of granulomas and endomysial thickening were noted in seven cases (14%); six cases (12%) being LL and one case (10%) being NL. Six cases (12%) showed degenerative changes associated with endomysial thickening, all of them being LL cases. Endomysial thickening was found in three cases (6%), all being of LL type.

DISCUSSION

The present study of 50 striated muscle biopsies from apparently healthy muscles without any evidence of atrophy or functional impairment revealed various types of pathologic lesions in a significant proportion of the cases in lepromatous leprosy.

Muscle necrosis was not a prominent feature in our cases. But wherever the granulomas closely abutted on the muscle fibers and showed a tendency to encroach upon them the muscle fibers showed necrosis. Job *et al* (⁴) have also reported similar findings. Some of the muscle fibers which were enclosed in larger granulomas also showed necrosis along with other degenerative changes.

Thickening of the endomysium reported by Convit *et al* (1) and Job *et al* (4) was also observed in this study more frequently in cases of lepromatous leprosy than in nonlepromatous cases (10%).

Although fibrosis was noted in and around inflammatory nodules, in no case was there total replacement fibrosis of muscle fibers. In the majority of cases there was broadening of perimysium and endomysium as was also observed by Convit *et al* (1).

The earlier workers who found that direct muscle involvement occurs in leprosy (1.3.4) chose their cases and sites of muscle biopsies after careful examination and deep palpation of muscle. Job et al (4) described leprosy lesions of striated muscles under three stages. The initial stage was of invasion and proliferation of acid-fast bacilli inside muscle fibers and tissue histiocytes. The second stage comprised degeneration of muscle fibers followed by infiltration with neutrophils, lymphocytes, macrophages, and the bacilli become fragmented and granular. In the third stage there was replacement of destroyed muscle fibers by fibrous tissue along with reconstitution of macrophages and total disappearance of bacilli. Our findings, in general, support this interpretation.

In view of the presence of granulomas in different locations in muscles it becomes slightly difficult to assume the route taken by the organisms to reach muscle fibers. In the presence of continuous bacteremia in untreated cases of lepromatous leprosy, it is reasonable to believe that bacilli reach muscles by hematogenous route. Even the presence of nodules in the perimysium and endomysium do not exclude this possibility

because of the fact that blood vessels lie in these coverings and also form capillary networks in the endomysium. Early lesions may appear in the endomysium and subsequently encroach upon the muscle fibers. Muscular lesions of other bacterial origin are rare, probably because of the frequent contractions of the muscle fibers which do not allow organisms to settle easily in muscle tissue and produce lesions. The metabolic products of muscle contraction may alter the internal environment in such a way as to prevent the growth of organisms, Mycobacterium leprae being an exception in this respect. It is stated that these bacteria can lodge in the striated muscle fibers and multiply. It has been observed that the leprosy bacilli could be identified, in the viable state, in muscle tissue of lepromatous leprosy patients under treatment, even after their skin biopsies became negative for bacilli (5). This may be due to some special chemical constituent of these bacilli or their metabolites which are not clearly elucidated so far. Such property of this organism and the continuous bacteremia observed in cases of lepromatous leprosy (2) throw doubt on the presumed predilection of this organism to inhabit the relatively colder parts of the human body.

It seems that *Mycobacterium leprae*, through the hematogenous route, get settled in muscle and lead to granuloma formation which gradually enlarge, coalesce and invade the muscle fibers leading to degenerative changes and necrosis followed by fibrosis in later stages.

SUMMARY

Histopathologic changes in striated muscle biopsies in 50 cases of leprosy were studied; 40 being the lepromatous type and 10 the nonlepromatous type. All the biopsies were obtained from midportions of normal looking biceps muscles and paraffin embedded. Sections cut in transverse and longitudinal planes were stained by hematoxylin and eosin, Masson's trichrome, Mallory's PTAH, Gomori's silver impregnation, and Ziehl-Neelsen's technic. Lepromas, focal or confluent, in the endomysium, perimysium, muscle fibers and perineurally, constituted the most common pathologic lesion, being observed in 34% of all cases with a higher frequency in the lepromatous type. Acid-fast bacilli could be demonstrated in some of

these lepromas. These nodules were observed even in younger patients and increased in frequency as the age of patient advanced. Three cases of nonlepromatous leprosy showed granulomas. Other changes noted in varying proportions were loss of striations, hyaline change, fatty change, sarcolemmal changes, along with endomysial thickening, muscle necrosis and fibrosis. Bacillemia in leprosy and the possible route of muscle invasion resulting in subsequent production of leprous nodules with associated degenerative changes, independent of nerve involvement, have been postulated.

RESUMEN

Se estudiaron las alteraciones histopatológicas en biopsias de músculo estriado en 50 casos de lepra; 40 del tipo lepromatoso y 10 del tipo nolepromatoso. Todas las biopsias se obtuvieron de la porción media de biceps de aspecto normal y se incluyeron en parafina. Los cortes se hicieron en forma transversal y los planos longitudinales se tiñeron con hematoxilina y eosina, tricrómico de Masson, PTAH de Mallory, impregnación de plata de Gomori y la técnica de Ziehl-Neelsen. Las lesiones patológicas más comunes fueron lepromas, focales o confluentes, en el endomisium, perimisium, fibras musculares y perineurales; se observaron en el 34% de los casos, con mayor frecuencia en el tipo lepromatoso. En algunos de estos lepromas, se observaron bacilos ácido-resistentes. Estos nódulos se observaron aún en pacientes jovenes y aumentaron en frecuencia a medida que la edad de los pacientes avanzaba. Tres casos de lepra no lepromatosa mostraron granulomas. Otros cambios observados en proporciones variables, fueron pérdida de estriamiento, alteraciones hialinas, alteraciones lipídicas, alteraciones sarcolemales, junto con engrosamiento endomisial, necrosis muscular y fibrosis. Se ha postulado la bacilemia en lepra y la posible ruta de invasión muscular, que resulta en la producción de nódulos de lepra con cambios degenerativos asociados, independientemente de compromiso nervioso.

RÉSUMÉ

On a étudié les modifications histopathologiques dans des biopsies de muscles striés obtenues dans 50 cas de lèpre, dont 40 étaient du type lépromateux et 10 du type non lépromateux. Toutes les biopsies ont été prélevées au niveau de la partie médiane de biceps d'apparence normale. Elles ont été enrobées dans de la paraffine. Les coupes sectionnées selon les plans transverse et sagittal ont été colorées par l'hématoxyline et l'éosine, le trichrome de Masson, le PTAH de Mallory, l'imprégnation argentique de Gomori, et la technique de Ziehl-Neelsen. La lésion pathologique la plus commune a consisté en lépromes, confluents ou en foyers, situés dans l'endomysium, le perimysium, les fibres musculaires, et autour des nerfs. Ce type de lésion a été observé dans 34 pour cent de tous les cas, et ceci plus fréquemment dans le type lépromateux. Dans quelques uns de ces lépromes on a pu mettre en évidence des bacilles acido-résistants. Ces nodules ont été observés même chez les malades les plus jeunes; ils étaient d'autant plus fréquents que l'âge du patient était plus avancé. Trois cas de lèpre non lépromateuse ont révélé des granulomes. Les autres modifications observées en proportions diverses étaient la perte de stries, des modifications hyalines, une transformation graisseuse, des modifications au niveau du sarcolemme de même qu'un épaississement de l'endomysium, de la nécrose musculaire, et de la fibrose. On doit admettre qu'une bacillémie se produit dans la lèpre, et qu'il existe une route possible d'invasion musculaire qui entraîne la formation ultérieure de nodules lépreux, associés à des modifications dégénératives, qui est indépendant de l'atteinte nerveuse.

REFERENCES

- CONVIT, J., ARVILA, J. J. and MENDOZA, S. Lepromatous myositis. Int. J. Lepr. 28 (1960) 417-422.
- DRUTZ, D. J., CHEN, T. S. N. and WEN-HSIANG LU. The continuous bacteremia of lepromatous leprosy. N. Engl. J. Med. 287 (1972) 159-164.
- ISHIHARA, S. Myositis interstitialis leprosa. Int. J. Lepr. 27 (1959) 341-346.
- JOB, C. K., KARAT, A. B. A., KARAT, S. and MATHAN, M. Leprous myocitis—A histopathological and electron microscopic study. Lepr. Rev. 40 (1969) 9-16.
- PEARSON, J. M. H., REES, R. J. W. and WED-DELL, A. G. M. *Mycobacterium leprae* in the striated muscle of patients with leprosy. Lepr. Rev. 41 (1970) 155-166.