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Pathological Findings on Peripheral Nerves, Lymph Nodes, and Visceral Organs of Leprosy[1]

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Others have reported the pathological findings in autopsies and biopsies in leprosy ([1, 3, 5]) but there are few reports from our country. This paper presents studies on pathological materials from leprosy patients which have been collected over a period of many years from the southern part of China. It also extends the findings of our first report, published in 1962, covering 34 necropsies ([8]).

MATERIALS AND METHODS

One hundred three autopsies on patients with various types of leprosy were examined, including 80 cases with lepromatous leprosy (LL), 21 cases with tuberculoid leprosy (TT), and 2 cases with borderline disease. In addition, 210 biopsies of TT peripheral nerves and 106 biopsies of inguinal lymph nodes with various types of leprosy were studied. All specimens were fixed in 10% formalin, embedded in paraffin, and sections were stained with hematoxylin and eosin (H&E) and the Wade-Fite stain for leprosy bacilli. Some sections were stained by the Sudan III method for lipids as well as by the Gormoi method for reticulin.

Based on the different pathological patterns of the lesions, we have also classified the various types of leprosy into three stages, i.e., progressive, regressive, and quiescent. These staging criteria have been applied to all the lesions examined.

RESULTS AND DISCUSSION

Peripheral nerve trunks and ganglia

Peripheral nerve trunks. A total of 1111 sections of nerve trunks were examined, taken from 93 autopsies, including 70 LL cases, 21 TT cases, and 2 borderline cases. The frequency of various nerve involvement is shown in Table 1. The most commonly affected nerves in sequence were the ulnar, peroneal, median, radial, great auricular, tibial, and the supraorbital.

In addition, specimens were obtained from the same nerve on both the right and left side of the body. Tissue blocks taken from 439 such pairs of the same nerve were examined. Among 314 pairs from lepromatous leprosy patients, 164 pairs (52.2%) were affected bilaterally; whereas 33 pairs (10.5%) were affected unilaterally. The ratio of bilateral to unilateral involvement was 5:1. Out of 113 pairs from tuberculoid leprosy patients, 42 pairs (37.2%) were affected bilaterally and 22 pairs (19.5%) unilaterally with a ratio of bilateral to unilateral involvement of 2:1. Out of 12 pairs of nerves from borderline lepromatous patients, the ratio of bilateral to unilateral involvement was the same (5:1) as in lepromatous leprosy.

In spite of the higher frequency of bilateral to unilateral nerve involvement in LL than in TT, the lesions were by no means generally and symmetrically distributed in the same nerve. Even though the ulnar, peroneal, and median nerves had the highest frequencies of involvement, there were still a number of cases without any lesion found, or with only unilateral involvement. Furthermore, as mentioned above, even in TT bilateral nerve trunk involvement was more frequent than unilateral nerve involvement.

Many authors have suggested that bilateral nerve involvement in LL is related to blood-borne dissemination; whereas frequent unilateral nerve lesions in tuberculoid leprosy are due to direct extension from the skin lesions which are usually distributed randomly or asymmetrically. However, Skinsnes and Yamashiro ([7]), demonstrating acid-fast bacilli in the endothelial cells of perineural and intraneural lymphatics, suggested that the nerve lesions possibly spread from skin lesions by lymphatic dissemination. Dastur, *et al.* ([2]) examined the histol-

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TABLE 1. *The frequency of nerve trunk involvement in leprosy autopsies.*[a]

Nerves	Type of leprosy		
	LL	TT	Borderline
Great auricular	43/52 (82.7)	8/17 (47.1)	2/2 (100)
Radial	41/50 (82)	12/18 (66.6)	2/2 (100)
Median	46/51 (90.2)	16/20 (80)	2/2 (100)
Ulnar	57/58 (98.3)	18/21 (85.7)	2/2 (100)
Brachial	2/22 (9.1)	3/10 (30)	
Intercostal	0/20 (0)	2/10 (20)	
Lumbar	1/8 (12.5)	2/4 (50)	
Sciatic	3/30 (10)	3/12 (25)	1/2 (50)
Popliteal	12/19 (63.2)	4/6 (66.7)	
Tibial	20/29 (69)	8/13 (61.5)	2/2 (100)
Peroneal	46/47 (97.9)	14/18 (77.8)	2/2 (100)
Femoral	2/20 (10)	1/7 (14.3)	
Supraorbital	2/2 (100)		
Cervical vagus	3/32 (9.4)	1/11 (9.1)	0/2 (0)

[a] Data are presented as numbers showing leprosy lesions/number of specimens examined (% involvement).

ogy of facial nerves in leprosy and found that the distal part was affected more severely than the proximal part. Our observations are similar. However, in 13 blocks of neural tissue without any lesions, we could find a few bacilli within neural fibrils. This evidence suggests that the bacilli may also spread along the nerve fibril from distal to proximal parts. In some of our tuberculoid cases, the vagus and brachial plexus nerves were involved, and these nerves have no known direct connection with the skin lesions. All in all, we have concluded that the lesions in peripheral nerves may spread by means of the blood stream and the lymphatic channels, as well as by direct extension within the nerve itself.

The histology of the nerve lesions in both polar types was the same as that seen in the skin, except that in TT the lesions were more apt to undergo caseation with the formation of the so-called "nerve abscess." Also, bacilli were more easily found in the epithelioid cells in the TT nerves compared with TT skin lesions.

TABLE 2. *Neural ganglion involvement in 36 cases of lepromatous leprosy.*

Ganglion	Severe lesion	Mild lesion	Normal
Spinal (19 cases)	7	7	5
Trigeminal (2 cases)	2	—	—
Cervical sympathetic (35 cases)	6	10	19
Celiac (20 cases)	—	7	13

The two cases of borderline leprosy showed different pathologic changes in the peripheral nerve trunks. One case showed the left median and right radial nerves in the progressive stage of lepromatous leprosy. However, the right median, left radial, and left great auricular nerve showed tuberculoid lesions. Moreover, the ulnar, right peroneal, and right auricular nerves bilaterally showed not only lepromatous lesions but also tuberculoid changes. We have described and published these findings in the past ([8]).

We compared the nerve lesions and the skin lesions in the same cases. Out of 25 cases of LL with skin lesions in the quiescent stage, 2 cases showed progressive stages in the nerve lesions; whereas in 23 cases, the nerve lesions were in a regressive stage. Out of 51 cases of TT with skin lesions in the quiescent stage, 12 cases had nerve lesions in a progressive stage and 39 cases in a regressive stage. Therefore, it seems that nerve lesions are slower to regress than skin lesions.

Leprosy lesions in neural ganglia. We examined the peripheral ganglia in 51 cases. Out of 36 cases of LL, 22 cases (61.1%) showed lesions in the ganglia. The mild lesion consisted of focal round cell infiltration and atrophy of some ganglion cells. Severe lesions might show ganglion cells in re-

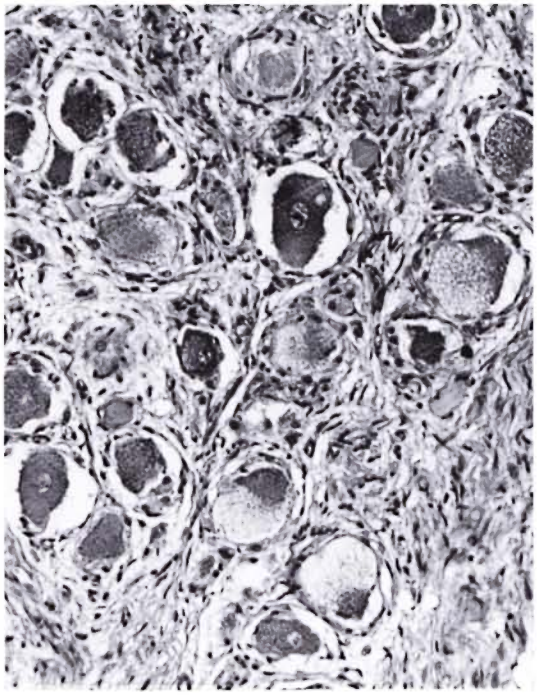

FIG. 1. Neural ganglion in LL. Many ganglion cells show swelling and foamy structure of cytoplasm with pyknosis and displacement of nuclei (H&E ×280).

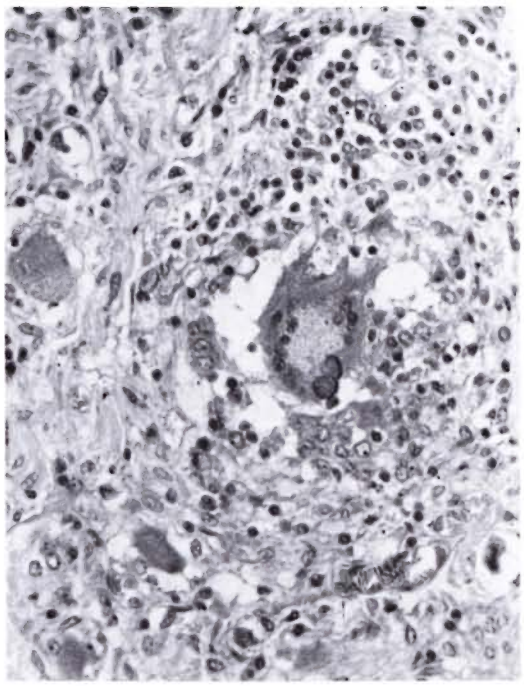

FIG. 2. Neural ganglion in TT. Tuberculoid lesion consists of Langhans' cells, epithelioid cells and lymphocytic infiltration (H&E ×280).

markable degeneration, with nuclear pyknosis and swelling of the cytoplasm which became rarified and appeared foamy in structure (Fig. 1). At times, leprosy bacilli could also be found. The results are summarized in Table 2. The trigeminal and spinal ganglion were most commonly involved, but lesions could also be found in sympathetic ganglia as well as in the celiac ganglion.

Out of 15 cases of neural ganglia which were examined in TT, pathologic changes were seen in 8 cases (53.3%), 2 in the spinal, 1 in the trigeminal, and 2 in the cervical sympathetic ganglia. All of them showed tuberculoid lesions consisting of epithelioid cells, some Langhans' giant cells, and lymphocytic infiltration (Fig. 2).

To date there are few records of leprous lesions in neural ganglia. The frequency of these lesions is so high in our study that it may prove valuable to pay more attention to these lesions, especially the correlation of the lesions with the clinical appearance. The lesions in neural ganglia may be due to direct spread from the peripheral nerve involved, or spread by the hematogenous route.

Lymph nodes

The involvement of lymph nodes in autopsies from 70 cases of LL and two cases of borderline leprosy are seen in Table 3. The superficial lymph nodes were mostly affected, probably being closely related to the skin lesions which they drained. In deep lymph nodes, the involvement was usually secondary to drainage from the affected organs. For example, the involvement of hepatic and splenic hilar nodes was always associated with leprous lesions in the liver and the spleen. For the same reason, the lungs were free of leprous lesions, and the pulmonary hilar nodes were not involved. The lesions in autopsies as well as in biopsies were composed of foam cells with bacilli forming large sheets within lymph nodes.

The lesions in 21 autopsies of TT were all in the quiescent stage so that no tuberculoid lesions were found in any lymph node examined. On the other hand, in biopsy specimens of inguinal lymph nodes in TT,

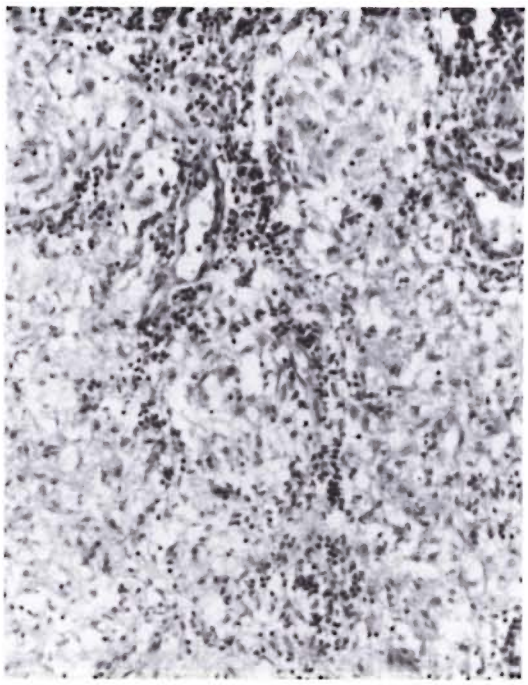

FIG. 3. Lymph node in BB. Foci of many epithelioid-foam cells confluent into a larger sheet (H&E ×200).

FIG. 4. Liver in LL. Proliferation of fibrous tissue around foci of foam cells, resulting in hepatic cirrhosis (H&E ×100).

out of 27 cases in which skin lesions were in a progressive stage, 19 cases (70.4%) showed the presence of leprous lesions in the lymph nodes with foci of epithelioid cells. A few lepra bacilli were found in three cases.

Thirty-seven biopsies of inguinal lymph nodes from borderline leprosy patients were examined. The skin lesions of all of them were in the progressive stage. Of 18 cases of BT examined, the lesions consisted mainly of epithelioid cell foci, occasionally mixed with some epithelioid-foam cells which contained the features of both epithelioid and foam cells. In 11 cases of BB, the lesions consisted of many epithelioid-foam cells which occasionally appeared in sheets (Fig. 3). In eight cases of BL, the lesions likewise consisted mainly of epithelioid-foam cells. Sometimes these were mixed with a foam cell infiltration and appeared as a large sheet located in the paracortex of the lymph node. More or less leprosy bacilli could be dem-

TABLE 3. *Frequency of lymph node involvement in lepromatous and borderline leprosy (autopsy cases).*[a]

Lymph node	Frequency of involvement
Cervical	42/49 (85.7%)
Axillary	36/42 (85.7%)
Elbow	10/12 (83.3%)
Inguinal	60/72 (83.3%)
Popliteal	10/12 (83.3%)
Hepatic hilar	15/19 (78.9%)
Splenic hilar	6/8 (75.0%)
Para-aortic	9/17 (52.9%)
Pulmonary hilar	0/7 (0%)

[a] Data are presented as numbers showing leprosy lesions/number of specimens examined (% involvement).

TABLE 4. *Incidence and distribution of lesions in respiratory tract.*[a]

Sites of lesions	Frequency of involvement
Nose	5/11 (45.5%)
Nasopharynx	8/22 (36.4%)
Larynx	19/34 (55.0%)
Trachea and bronchi	4/33 (12.1%)

[a] Data are presented as numbers showing leprosy lesions/number of specimens examined (% involvement).

onstrated in all of the borderline cases examined. The Sudan IV stain showed a slight positive in BT cases. In BB or BL cases the positive reactions were much stronger.

The lesions of the lymph node in the various types of leprosy are apparently similar to those seen in skin ([4, 6]). In borderline leprosy these lymph node lesions show a spectrum-like pattern between the two polar types and probably reflect the variability of the immunological condition of the host in the various types of leprosy.

Leprosy lesions in the viscera

Eighty autopsy cases of lepromatous leprosy.

Respiratory tract. The incidence and distribution of leprous lesions are seen in Table 4. The lepromatous lesions mainly involved the larynx and the parts above it. The foam cells infiltrated not only in the mucous membrane, but also along or invaded into the small nerve bundles, blood vessels cartilage, and vocal muscles. Eight cases showed infiltration of foam cells in the nasopharynx which, so far as we know, has been seldom reported before.

Digestive tract. Out of 30 cases in which the oral mucous membrane was examined, only four cases (13.3%) had infiltration of foam cells with a few leprosy bacilli in them.

Liver. Out of 75 cases examined, 64 cases (85.3%) had leprous lesions. Foam cells forming miliary lepromas were found in the portal areas or in the sinus near the central veins. Moreover, Kupfer cells often showed hyperplasia with foamy appearance and some bacilli could be found in their cytoplasm. According to the patterns of the lesion, 23 cases were in the progressive stage, 26 cases in the regressive stage, and 15 cases in the quiescent stage. In addition, proliferation of fibrous tissue might occur in or around the lesions (Fig. 4) of the regressive or quiescent stages. In three cases, typical "pseudolobules" were found. We believe that this was the result of fibrosis and that it could evolve into hepatic cirrhosis. There were three cases in which the skin lesions were in a quiescent stage, while the liver still remained in a regressive stage. This demonstrated that the leprous lesions in the liver diminished more slowly than those in the skin of the same cases.

Spleen. Out of 73 cases examined, 30 cases (41.1%) showed foam cells forming lepromas in the splenic medulla.

Bone marrow. Out of 46 cases examined, in four cases (8.6%) we could find miliary lepromas within bone marrow tissue.

Testicle and epididymis. Out of 45 cases examined, lepromatous lesions could be found in 39 cases (86.7%). Seven cases were in the progressive stage in which interstitial tissue was seen infiltrated by foam cells, and the spermatopoietic epithelia of the tubules showed obvious atrophy. There were two cases associated with lepromatous reaction, polymorphonuclear leukocytes being seen in the interstitial tissue forming small abscesses. In 25 cases in the regressive stage and seven cases in the quiescent stage, the interstitial tissue and the tubules showed obvious hyalinization. Out of 23 specimens of epididymis examined, 13 cases showed lepromatous lesions.

Adrenal gland. There was foam cell infiltration and scarce bacilli in 21 specimens (34.4%) of adrenal glands among 61 cases examined. The lesions were more frequently located in the area between the cortex and the medulla.

Eyeball. Out of 27 cases examined, 3 cases had leprous cyclitis and 1 showed sclera with miliary lepromas.

Additionally, we examined the lungs in 78 cases, the heart and the aorta in 76 cases, the esophagus and gastrointestinal tract in 68 cases, the kidney and bladder in 74 cases, the pancreas and biliary tract in 55 cases, the thyroid in 72 cases, the parathyroid in 5 cases, the brain and spinal cord in 70 cases, as well as the hypophysis in 64 cases. We could not find any leprous lesions in any of these tissues or organs.

Tuberculoid leprosy autopsies. In 21 autopsies of tuberculoid leprosy, no leprous lesions were found in any of the following organs examined: respiratory tract, digestive tract, liver, heart, kidney, adrenal, thyroid, brain, spinal cord, and eyeball. Whether the tuberculoid leprous lesions had disappeared before autopsy or not could not be determined since these cases were all following treatment for years.

Borderline leprosy autopsies. In two cases of borderline leprosy, biphasic leprous lesions were found in different organs and in the peripheral nerves. In the first case the nasal membrane showed lepromatous le-

sions, but the testicle showed biphasic lesions which consisted not only of epithelioid cells but Langhans' giant cells. The other case showed lepromatous lesions in bone marrow; whereas the liver showed biphasic lesions and, particularly, tuberculoid foci were found in cardiac muscle.

Causes of death in 103 autopsies

In our material there were no instances in which death was due to leprous lesions directly. In all of the cases death resulted from serious complications occurring during the course of the disease. There have been many reports ([1]) concerning the causes of death among leprosy patients in the literature, but the results have been quite different from various countries. In the present study, the causes of death in the 103 autopsies were analyzed mainly by pathological changes. We found tuberculosis (24 cases, 23.3%) to be the most common cause of death. Acute pulmonary infections (15 cases, 14.6%) was the second most frequent cause of death, while hepatic diseases (12 cases, 11.6%) and malignant tumors (10 cases, 9.7%) ranked third and fourth, respectively. These results are considerably different from past European and American reports ([1, 3, 5]) which found renal insufficiency due to amyloidosis to be the most common cause of death in leprosy. In our series only one lepromatous case died from renal insufficiency due to amyloidosis.

SUMMARY

Pathological findings in a) 103 autopsies, b) biopsy material of peripheral nerve tissue from 210 tuberculoid patients, and c) inguinal lymph nodes from 106 leprosy cases are presented. Overall, lesions in peripheral nerves were most common in the ulnar (85.7% in the TT type, 98.3% in LL), peroneal (77.8% in TT, 97.9% in LL), median (80% in TT, 90.2% in LL), radial (66.6% in TT, 82% in LL), and the great auricular, tibial and supraorbital nerves. The ratio of bilateral nerve involvement in the same nerve was higher than unilateral involvement (approximately 5:1). Lesions of the peripheral nerve ganglion were seen in the LL type (22 cases, 61.1%) and the TT type (8 cases, 53.3%). These have seldom been mentioned in past literature.

Superficial lymph nodes were most commonly affected in all types of leprosy. Lymph nodes in the hepatic and splenic portal areas were sometimes involved in lepromatous or borderline cases. Between the two polar types of leprosy, the lesions in the lymph nodes showed gradual transitions in a spectrum-like pattern which were similar to the changes in the lesions in the skin.

In lepromatous leprosy, lesions could be found in 85.3% of the cases in the liver, 41.1% in the spleen, 86.7% in the testes, approximately 50% in the upper respiratory tract (including 36.4% in the nasopharynx), and 34.4% in the adrenal gland. Three cases had ophthalmologic lesions. In borderline leprosy, biphasic lesions of leprosy were found in various internal organs. The development of hepatic cirrhosis in some patients could have connection with lepromatous lesions of the liver.

The lesions shown in each type of leprosy were divided into three different stages, i.e., progressive, regressive, and quiescent. In some cases the regressive changes seen in the visceral or peripheral nerve lesions were remarkably slower than those in the skin.

The most common causes of death in our 103 cases were tuberculosis (23.3%), acute pulmonary infections (14.6%), various hepatic diseases (11.6%), and cancer (9.7%). In only one case was death due to renal insufficiency due to severe renal amyloidosis.

RESUMEN

Se describen los hallazgos patológicos observados en (a) 103 autopsias, (b) 210 biopsias de tejido nervioso periférico de pacientes tuberculoides, y (c) 106 ganglios linfáticos inguinales de pacientes con lepra. De manera general, las lesiones en los nervios periféricos fueron más frecuentes en el ulnar (85.7% en TT, 98.3% en LL), en el peroneal (77.8% en TT, 97.9% en LL), en el mediano (80% en TT, 90.2% en LL), en el radial (66.6% en TT, 82% en LL), y en los nervios gran auricular, tibial y supraorbital. La afección bilateral de un nervio fue más frecuente que la unilateral (aproximadamente 5:1). Se observaron lesiones de los ganglios nerviosos periféricos en el tipo LL (22 casos, 61.1%) y en el tipo TT (8 casos, 53.3%). Esto rara vez se encuentra mencionado en la literatura.

En todos los tipos de lepra, los ganglios linfáticos superficiales fueron los más comunmente afectados; en algunas ocasiones también se vieron afectados los ganglios linfáticos de las áreas portales hepática y esplénica de los casos lepromatosos e intermedios. Entre los dos tipos polares de lepra, las lesiones en los ganglios linfáticos mostraron transiciones graduales, a manera de

un espectro, que fueron similares a los cambios en las lesiones dérmicas.

En la lepra lepromatosa se encontraron lesiones en el hígado en el 85.3% de los casos, en el bazo (41.1%), en testículos (86.7%), en el tracto respiratorio superior (50%) incluyendo nasofaringe (36.4%), y en las glándulas adrenales (34.4%). Tres casos tuvieron lesiones oftalmológicas. En la lepra intermedia se encontraron lesiones bifásicas en varios órganos internos. En algunos pacientes, el desarrollo de cirrosis pudo estar relacionado con las lesiones lepromatosas en el hígado.

Las lesiones mostradas en cada tipo de lepra fueron divididas en 3 clases: progresivas, regresivas, y quiescentes. En algunos casos, los cambios regresivos notados en las lesiones viscerales o en los nervios periféricos ocurrieron en forma más lenta que en la piel.

Las causas más comunes de muerte fueron: tuberculosis (23.3%), infecciones pulmonares agudas (14.6%), diversas enfermedades hepáticas (11.6%), y cáncer (9.7%). Sólo en un caso la muerte se debió a insuficiencia renal secundaria a amiloidosis severa.

RÉSUMÉ

On présente ici les observations pathologiques recueillies a) lors de 103 autopsies; b) dans du matériel de biopsie des tissus nerveux périphériques chez 210 malades tuberculoïdes; et c) dans des glanglions lymphatiques inguinaux de 106 cas de lèpre. Dans l'ensemble, les lésions des nerfs périphériques étaient plus fréquentes au niveau des nerfs cubital (85,7% dans le type TT, 98,3% dans le type LL), péronier (77,8% dans le type TT, 97,9% dans le type LL), médian (80% dans le type TT, 90,2% dans le type LL), radial (66,6% dans le type TT, 82% dans le type LL), de même que dans le grand auriculaire, le tibial et les nerfs sus-orbitaux. Le ratio de l'atteinte nerveuse bilatérale dans le même nerf était plus élevé que l'atteinte unilatérale (environ 5 à 1). Des lésions des ganglions nerveux périphériques ont été relevés dans le type LL (22 cas, 61,1%), et dans le type TT (8 cas, 53,3%). Ces lésions ont rarement été mentionnées dans la littérature.

Les ganglions lymphatiques superficiels étaient plus fréquemment atteints, et ceci dans tous les types de lèpre. Les ganglions lymphatiques au niveau des régions portales hépatique et splénique étaient parfois affectés dans les cas lépromateux et dimorphes. De l'une à l'autre extrémité du spectre de la lèpre, allant d'un type polaire à l'autre, les lésions des ganglions lymphatiques ont présenté une transition progressive parallèle aux modifications que l'on observe au niveau des lésions cutanées.

Dans la lèpre lépromateuse, des lésions pouvaient être trouvées chez 85,3% des cas au niveau du foie, 41,1% dans la rate, 86,7% dans les testicules, et environ 50% dans le système respiratoire supérieur (y compris 36,4% dans le nasopharynx), et 34,4% dans les glandes surrénales. Trois cas souffraient de lésions ophtalmologiques. Dans la lèpre dimorphe, des lésions biphasiques de lèpre ont été observées dans divers organes internes. Le développement d'une cirrhose hépatique chez quelques malades pourraient avoir un rapport avec les lésions lépromateuses du foie.

Les lésions observées dans chaque type de lèpre pouvaient être divisées en trois différents stades d'évolution, à savoir une évolution progressive, une évolution régressive, et un stade quiescient. Chez quelques malades, les changements regressifs constatés au niveau des lésions nerveuses viscérales ou périphériques étaient remarquablement plus lents que les modifications observées dans la peau.

Les causes les plus fréquentes de décès dans ces 103 cas ont été la tuberculose (23,3%), des infections pulmonaires aiguës (14,6%), diverses maladies hépatiques (11,6%), et le cancer (9,7%). Dans un cas seulement la mort a été due à une insuffisance rénale faisant suite à une amyloidose prononcée du rein.

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