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Malignant Lymphomas in Leprosy Patients
A Clinical and Histopathologic Study[1]

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A number of papers, by various authors, have been written on the association of cancer and leprosy ([10, 11,15]). This is not the case, however, with respect to malignant lymphoma and leprosy. It has been said that cancer is less frequent, more frequent, or the same as in the population free from leprosy, and several papers have been published in support of each of these arguments ([3, 6, 8, 12]).

Bosq ([2]), in 1955, reported the first case cited in the literature on the association of lymphoma and leprosy, and recently a case of postmortem finding of this association was reported by Takahashi *et al.* ([14]).

In the Sommer Colony, in the Province of Buenos Aires, Argentina, five patients have been found who were suffering from the combination of leprosy and lymphoma. This colony was founded in 1942 and some 3,000 patients have attended during the last 24 years. Five of the cases that we shall discuss were discovered and followed during the period 1958-1965. During this period 1,200 patients attended the colony. The sixth patient was followed at the Instituto Municipal de Hematologia. We would like to note here that the clinical histories of the patients who attended the colony between 1942 and 1958 were not written by hematologists, but by leprologists, so that during our revision of these records we could not find any data that might bring to light further cases.

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Case 1. (M.V.M.H.S., No. 1527). Female, born in 1902 in the Province of Buenos Aires.

1939. Probable onset of leprosy.
1949. 48 years old. Interned in the colony, suffering from leprosy, type L3. Positive bacilloscopy was noted, with disseminated leprous lesions, neural disturbances, destruction of the nasal septum, and amaurosis.
1953. Erythema nodosum, neuralgias of the ulnar nerve, and menopausal amenorrhea.
1954. Erysipelatous reaction of the feet.
1955. Erythema nodosum and febrile episodes.
1956. Reactions of skin and eyes. Bacilloscopy negative since 1957. No nodes palpable on internment, with the exception of those in the inguinocrural region, which were very small. Hepatomegaly and high blood pressure.
1961. November: An ovoid-shaped tumor appeared in the right axillary region; this reached the pectoral border and was painful on palpation. Antibiotics were administered for one month without any improvement. Surgical biopsy was performed, with resection of the conglomerate nodes adherent to the deeper tissue. Histopathologic study showed reticular lymphoblastic lymphoma.
1962. March: Radiotherapy started. Retroperitoneal pelvic tumor with anemia and general poor condition. Nitrogen mustard treatment commenced. Patient died on 21 August 1962.

Histopathologic report. *Macroscopic:* The glands of the whole group were enlarged. The cut surface showed a replacement of the normal structure by a yellowish-gray tissue. *Microscopic*: Sections showed complete destruction of normal gland structure and replacement by proliferation of lymphoblastic and reticular elements, passing the capsular borders and infiltrating the adjacent adipose tissue. In some regions there was a fibrotic process with signs of hyalinization; in others there were new hemorrhagic foci. Cytologic examination revealed a moderate amount of mitosis. Foci were found in reticular cells in macrophage activity (Figs. 1, 2). The findings in a second biopsy in this case were similar to those of the first.

Summary. Malignant lymphoma in a patient with 22 years of evolution of leprosy. She was treated on several occasions with chaulmoogra oil and sulfones, as well as with corticosteroids and antibiotics. The histopathologic diagnosis was reticular lymphoblastic lymphoma with some macrophage activity (II degree).

Case 2. (M.V.C., No. 2233). Female, born in 1915 in the Province of Chaco, Argentina.

1939. Probable onset of disease.

1954. 39 years old. Interned with L3 type leprosy. Positive bacilloscopy. Diffuse infiltration, and pigmented lesions with cutaneous and cicatricial atrophy of the limbs. Alopecia of eyebrows. Amenorrhea since 1944.

1954. October: Tumor measuring 3 x 2 cm. near the left breast. Surgical biopsy, with resection of lymph-nodes from left axilla in December of the same year. The histopathologic diagnosis was malignant lymphoma. Liver and spleen within normal limits. No other glands palpated. Good general condition. Subfebrile. Hemogram normal. Bacilloscopy negative.

1955. February: Patient started on nitrogen mustard. Good general condition. Thorax normal. June: hemoptoic sputum.

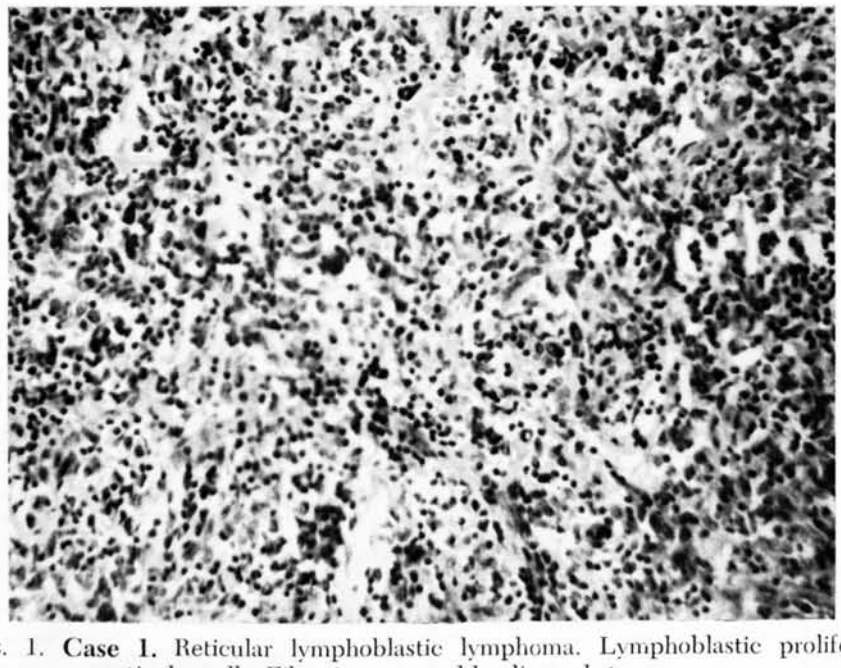

FIG. 1. **Case 1.** Reticular lymphoblastic lymphoma. Lymphoblastic proliferation with numerous reticular cells. Fibrotic areas and hyaline substance.

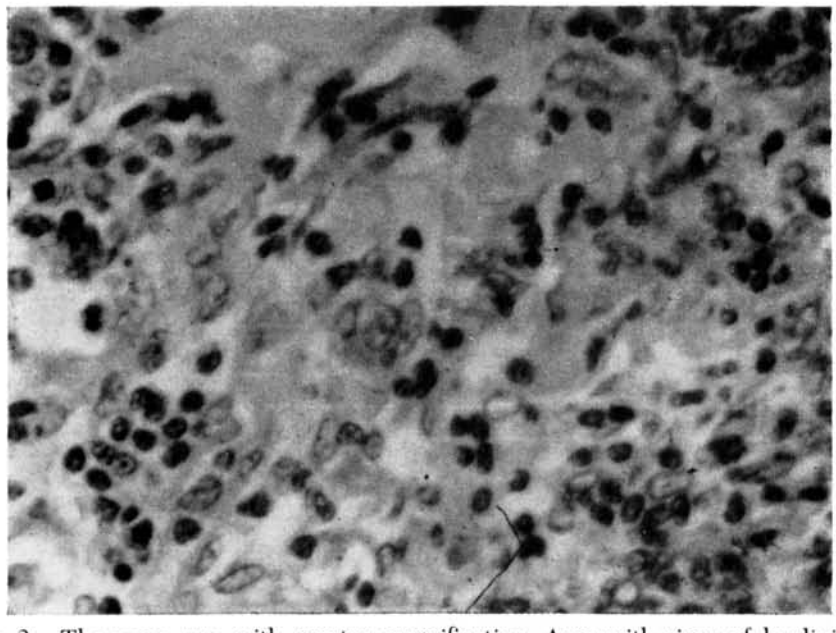

FIG. 2. The same case with greater magnification. Area with signs of hyalinization.

1956. Good general condition. Bacilloscopy has been negative for two years, but has now returned to positive. Biopsy of node in left axilla led to diagnosis of "glandular hyperplasia containing Virchow's cells." Patient treated with sulfones; various series administered up to 1965.

1965. October: Patient died from progression of the leprosy, but there were no signs of lymphomatous disease.

Histopathologic report. *Macroscopic:* An enlarged gland with clearly defined borders was studied; the increased size was related to a fairly firm cellular tissue. *Microscopic*: Sections showed a considerable increase in lymphoid follicles (Fig. 3), representing hyperplasia of the follicular elements. There were some large isolated reticular cells (Fig. 4). Some specimens showed abundant hyaline material. Very little macrophage activity. Some of the specimens showed obliteration of the follicular structure.

Summary. Macrofollicular lymphoma (lymphoblastic and reticular) in a 39 year old female, which appeared 15 years after the onset of leprosy. The tumor mass was resected and the patient was treated with nitrogen mustard. She died 11 years later of leprosy.

Case 3. (M.G., No. 2070). Male, native of the Province of Misiones, Argentina.

1951. Probable onset of leprosy.

1953. 31 years old. Interned, with L2 type of leprosy. Positive bacilloscopy. Lepromas on all four limbs. Torpid ulcers and generalized microadenopathies.

1960. January: Febrile leprous reaction, enlarged lymphnodes, generalized patches and macules. Aphonia. Intensive treatment started with sulfones, which was followed by great improvement. November: Patient had increased 12 kgm. in weight.

1962. April: Enlarged nodes in axillary and inguinal regions. Anti-inflammatory treatment given, with no improvement. Nodes continued to grow.

1963. July: Enormous tumors in the right abdomino-inguinal region. Surgical resection. The histopathologic diagnosis was Hodgkin's sarcoma (Figs. 5, 6). August: Radioactive cobalt therapy given, 5,500 r, to tumor in two inguino-crural fields in a period

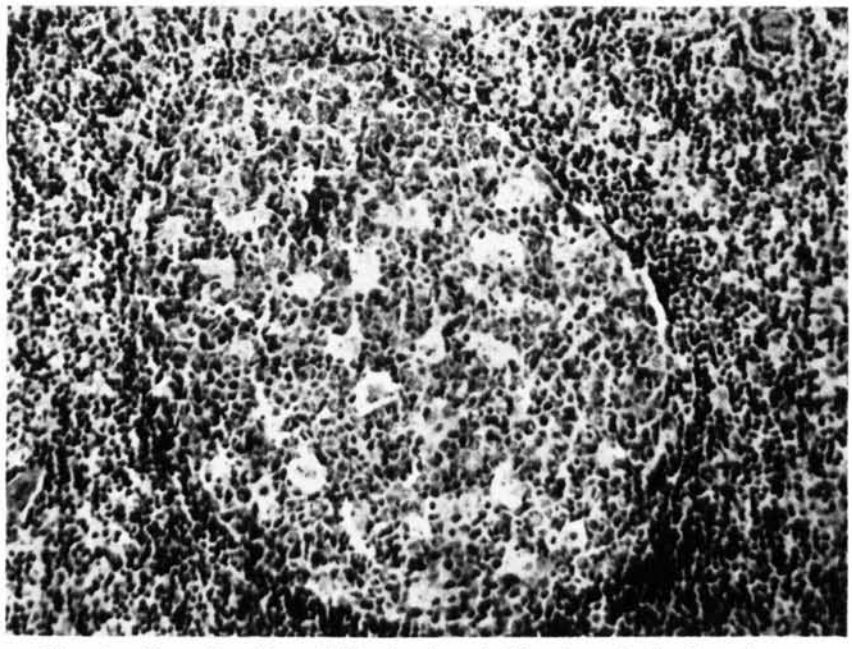

FIG. 3. **Case 2.** Macrofollicular lymphoblastic reticular lymphoma.

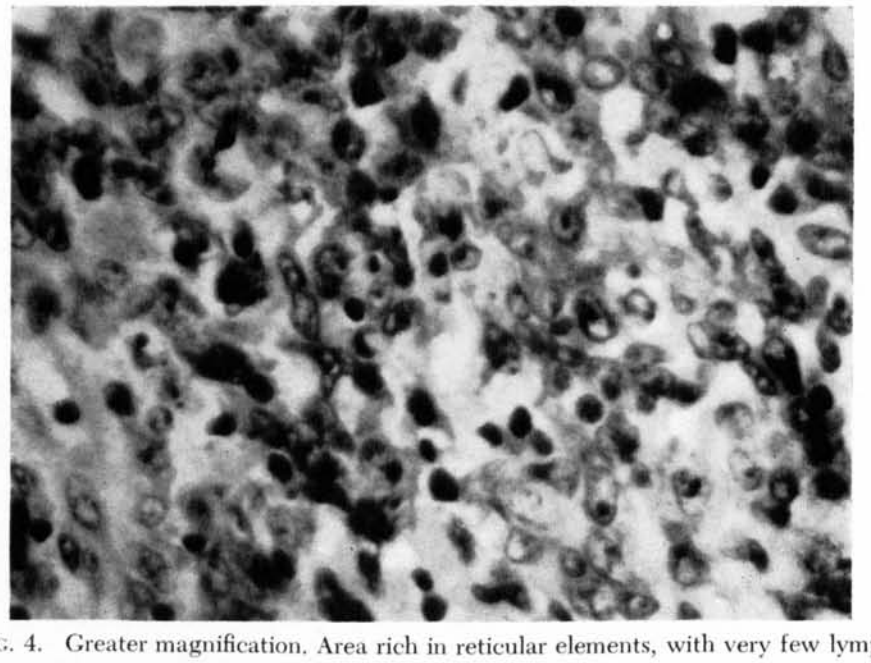

FIG. 4. Greater magnification. Area rich in reticular elements, with very few lymphocytes.

of 60 days. The tumor rapidly decreased in size. At intervals during the same period 4 gm. of cyclophosphamide was administered. November: 2 cm. node in left axilla; fever and anemia.

1964. February: Splenomegaly and abdomino-pelvic adenopathies. Patient treated with Vinblastin, 10 mgm. every 10 days, and prednisone 20 mgm. daily. His condition worsened after he received 50 mgm. of Vinblastin, with adenomegaly and hepatosplenomegaly. May: Intravenous methylhydrazine commenced. June: Jaundice, anemia, accelerated erythro-sedimentation rate, and severe hepatomegaly. Liver puncture showed lepromatous leprosy. August 20: Patient died in hepatic coma. Positive bacilloscopy. Generalized lymphoma.

Summary. This patient developed a progressive Hodgkin's sarcoma 11 years after the onset of lepromatous leprosy. He was treated by surgical resection, radioactive cobalt, cyclophosphamide, prednisone, Vinblastin and methylhydrazine, with unfavorable results. He died in hepatic coma with lepromatous leprosy of the liver.

Case 4. (G.J.N.L., No. 2771). Male, born in 1931 in the Province of Santa Fe, Argentina. Mother had leprosy.

1945. Probable onset of leprosy.

1958. Interned, with L2 type leprosy. Bacilloscopy negative. Examination showed macular lesions of all limbs with slight infiltration, atrophic scars, and remains of ulcers on the patient's arms. Perforation of the nasal septum. Skin anesthesia and several febrile leprous reactions. Microadenopathies. Spleen and liver within normal limits. Treatment with sulfones, with good results.

1960. May: Bilaterial cervical adenopathy, hepatosplenomegaly, enlarged mediastinum. Puncture biopsy of gland showed typical cytology of Hodgkin's disease. July: Surgical resection; diagnosis of Hodgkin's lymphogranuloma. August: Patient started on cyclophosphamide; received a total of 3.5 gm., which was badly tolerated. September: Glands of the axilla greatly increased in size. A new biopsy showed reticular hyperplasia with Virchow cells.

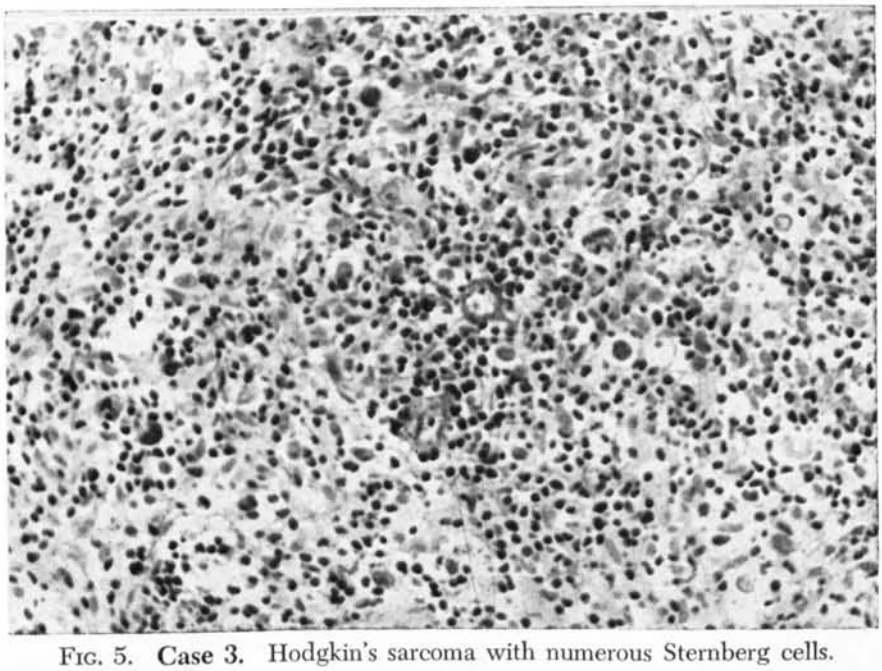

FIG. 5. **Case 3.** Hodgkin's sarcoma with numerous Sternberg cells.

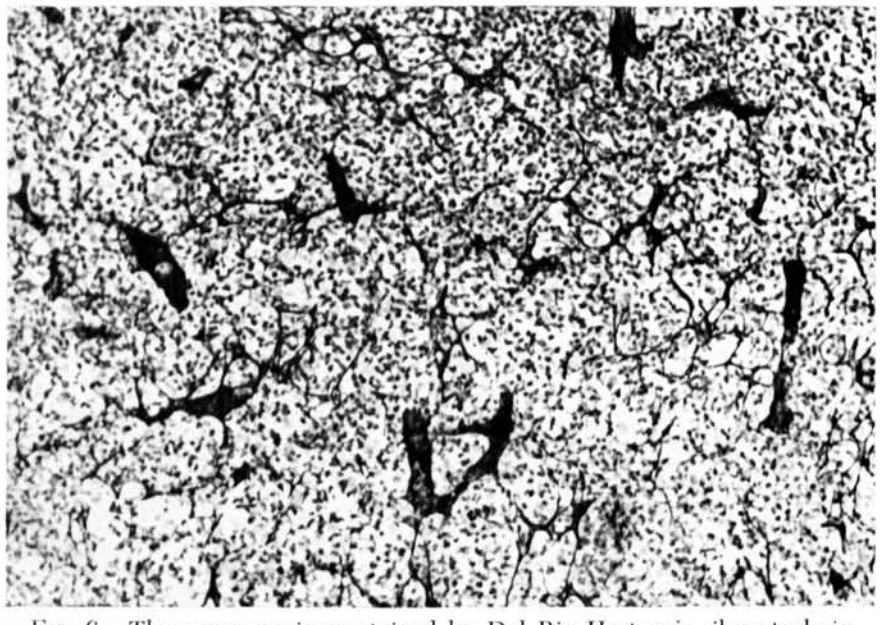

FIG. 6. The same specimen stained by Del Rio Hortega's silver technic.

1961. January: Mediastinal enlargement still present, with polyadenopathies and splenomegaly. Radiotherapy, 30 applications, with regression of tumor. Between October 1961 and March 1962, the patient received 25 ampoules of nitrogen mustard.

1962. April: Severe pruritus, mediastinum free, osteolysis of ribs. Abdominal tumor in right iliac fossa. Treatment with Bayer E 39 (1,200 mgm.), with no improvement. May: Osteolysis of humerus. Chlorambucyl treatment started, 10 mgm. daily. Radiation (7,000 r) because of growth of the abdominal tumor was given. Pruritus disappeared. Progress of disease continued. Treatment with nitrogen mustard, methylhydrazine, Vinblastin, and mustard uracil, without effect.

1964. August: Positive bacilloscopy, pruritus, fever, anemia and renal insufficiency until death in October 1964.

Histopathologic report. *Macroscopic:* Enlarged gland, which, when cut, showed large areas of fibrous tissue and, in these areas, foci of lymphoid tissue and adipose elements. Specimens taken from different layers and embedded in paraffin for preparation of sections. *Microscopic*: Hematoxylin and eosin staining showed areas of hyalinized fibrosis in the greater part of the material. The lymphoid areas showed combined proliferation of lymphocytes and reticular cells, some of these differentiating into Sternberg-type elements. Eosinophilic cells also were found in these sections, completing the picture of a granuloma. *Diagnosis*: Hodgkin's disease (Hodgkin's granuloma), with marked tendency toward hyalinization and fibrosis.

Second biopsy. *Macroscopic:* Moderate enlargement of the gland. On cutting, the parenchyma was found to show slight lipomatous impregnation, and soft consistency. *Microscopic*: Sections showed an accentuated infiltration of mature lipoblastic elements in the gland tissue. Among these, cellular, lymphoid and hyperplastic elements could be seen. There were foci of sclerosis and congested areas in other parts of the parenchyma. No bacilli were demonstrated with Ziehl-Neelsen staining. *Diagnosis*: Reactional adenitis with marked lipomatous infiltration and lymphoid hyperplasia.

Summary. Twenty-seven year old male who had been suffering from leprosy for

some 12 years at the time of internment. Three years later he developed Hodgkin's disease with enlarged mediastinal glands and hepatosplenomegaly. The response to various cytostatic drugs was good, but of short duration.

Case 5. (A.A., No. 1777). Male, born in Syria in 1911.

1948. Onset of leprosy.
1951. 40 years old. Interned, suffering from neural cutaneous L1 type leprosy with positive bacilloscopy, disseminated macules and hypochromic scars on the trunk.
1958. Adenopathy in the submaxillary angle bilaterally. Partial regression under antibiotic treatment. Biopsy because of persistence of enlargement of lymph nodes; the histopathologic diagnosis reported was lymphoblastic lymphoma. Under sulfone treatment the bacilloscopy had become negative. Nitrogen mustard treatment commenced. A month later lymph node enlargement with hepatosplenomegaly was noted. The patient refused radiotherapy.
1959. Nitrogen mustard was of no benefit.
1961. February: An additional biopsy of the gland confirmed the first diagnosis. July: Another series of cytostatic (cyclophosphamide) treatments was commenced, but without favorable result. December: mediastinal enlargement. Vinblastin administered. Patient died from hemoptysis of unknown cause.

Histopathologic report. *Macroscopic:* Enlarged gland (4 x 3 cm.), which showed a homogenous structure represented by lymphoid-like tissue. *Microscopic:* Examination of sections stained with hematoxylin and eosin showed complete destruction of the normal follicular pattern, which was replaced by lymphoblastic proliferation with isolated reticular elements and some lymphocytic cells (Fig. 7). *Diagnosis:* Lymphoblastic lymphoma.There were no signs of fibrosis and there was only a moderate amount of macrophage activity.

Summary. A 40 year old male whose leprosy had started 10 years before a diagnosis of lymphoblastic lymphoma was made, and who later developed splenomegaly and mediastinal enlargement.

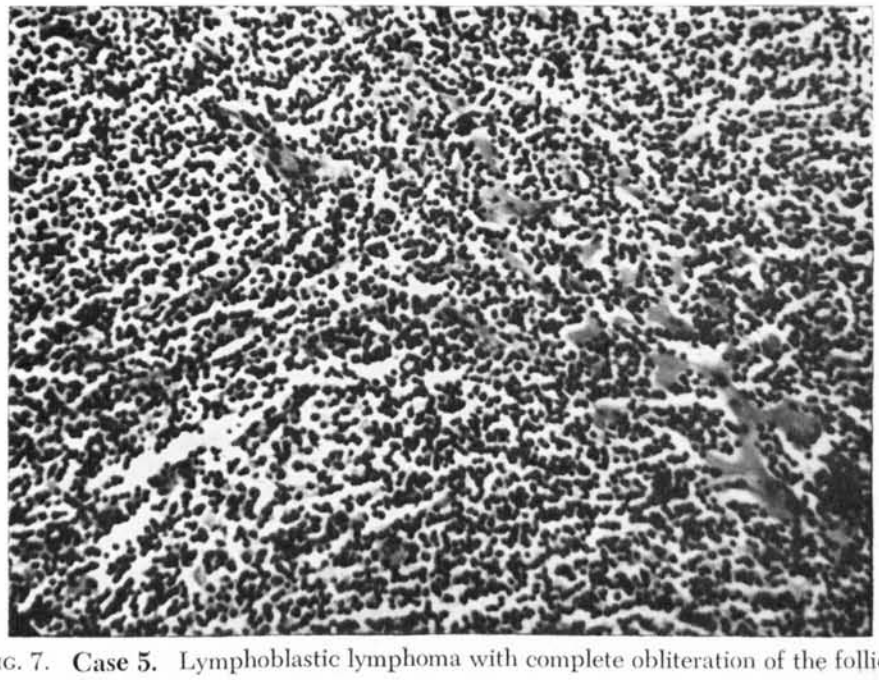

FIG. 7. **Case 5.** Lymphoblastic lymphoma with complete obliteration of the follicular structure.

Death occurred as a result of hemoptysis three years after the lymphoma appeared.

Case 6. (F. de R., No. 1961). 70 year old male, Italian. Enlargement of the glands of the axilla was noted, as the first sign of illness, in 1963. A diagnosis of lymphoblastic lymphoma was made from a biopsy specimen. The patient was treated with prednisone, and after January with Chlorambucyl. Progress was satisfactory until July 1965, when an erythematous plaque was discovered on the patient's back, with neither pruritus nor pain. As it was painless, a biopsy was performed, and a diagnosis of "tuberculoid leprosy of the skin of the back" was made. A biopsy of a node in the axilla confirmed the diagnosis of lymphosarcoma. A culture was negative for tubercle bacilli. No acid-fast bacilli were found, nor any Virchow cells. At the present time the patient has no clinical signs of leprosy, but slight enlargement of the axillary lymph nodes persists.

Histopathologic report. *Macroscopic:* Much enlarged glands (4 x 3 cm.). Cut surfaces showed a cellular type appearance with extensive necrosis. The borders were not well defined and were associated with fibrotic areas. *Microscopic*: Normal gland structure completely replaced by active proliferation of lymphoblastic elements. Mitotic activity in many sectors. There was cellular necrosis in other areas, with crystals of cholesterol. A poorly defined capsule was seen, with new fibrous tissue formation. Little macrophage activity was noted. *Diagnosis*: Lymphoblastic lymphoma.

DISCUSSION

Adenopathies, in which lymph nodes are sometimes very large, are frequently found in leprous patients, especially in its lepromatous form ([8]). Lymph nodes are palpable even in patients whose disease is quiescent ([1]). Lymphoreticular and plasmocyte hyperplasia are habitually found ([4, 13]). The five patients studied at Colonia Sommer suffered from lepromatous leprosy for 10, 11, 12, 15 and 22 years before the first signs of a lymphoma appeared. Their clinical evolution and treatment were similar to the course and therapy in other patients not suffering from leprosy. Their recurrences and complications were the usual ones and we could find no changes in the course of the disease that could be imputed to the lymphoma. Delayed hypersensitivity reactions were not observed, and, later, lymphocytic transfer from donors sensitive to specific antigens (tuberculin, histoplasmin and lepromin) did not sensitize the patients ([9]). From the histopathologic point of view the cases presented were typical of malignant lymphoma.

The patient in Case No. 6, in contrast with the other five, developed a tuberculoid form of leprosy two years after the onset of a lymphoma. After treatment, the lymphoma regressed, as often occurs. The leprosy lesions also disappeared with specific sulfone treatment.

Although the number of our cases is perhaps insufficient for general conclusions, the high proportion of fibrohyaline material in our series is worth considering. We can relate this material, in some degree, to the remarkable frequency with which amyloidosis is present in patients suffering from leprosy. Perhaps in some cases the hyaline material could be interpreted as being para-amyloid, not easy to detect histochemically.

An interesting observation was the lack of association in the lymphomatous glands with lepromatous granuloma and Virchow-type histiocytic cells with bacilli. This behavior is in direct contrast to the relative frequency with which a tuberculous granuloma is found in patients suffering from Hodgkin's disease when both diseases are present. The case of follicular lymphoma (Case 2) is remarkable, as this disease is found infrequently in this country. As is customary in this type of lymphoma, the evolution was prolonged.

The evolution of the six cases of malignant lymphoma in patients suffering from leprosy was in accord with their clinical form and histopathologic characteristics.

As respects the five cases of lymphoma found in 1,200 patients in a leprosy colony, it may be noted that this would appear to be an abnormally high proportion for a systemic disease not often associated with

leprosy. It is not possible, however, to draw any conclusions of statistical value. For this purpose it would be necessary to investigate every case of adenopathy found in patients suffering from leprosy.

We agree with Long ([5]), who wrote that "positive information on the subject is slender, and it will not be surprising if a long time is required to reach a satisfactory conclusion relative to the frequency of the association of lymphomas and leprosy."

SUMMARY

Six patients suffering from leprosy developed malignant lymphomas during the course of their illness. Five of them were members of the same colony. They represent the first finding of this type of association. Clinical and histopathologic studies showed the usual evolution of each disease. We believe that a fibrohyaline material found in the histologic sections may correspond to para-amyloid.

One remarkable fact is that in all of these cases the malignant lymphoma appeared many years after the apparent time of onset of leprosy, which ranged from 10 to 22 years.

It is suggested that this association may be frequent, and that all adenopathies found in leprosy patients should be investigated.

RESUMEN

Seis pacientes enfermos de lepra desarrollaron linfomas malignos durante el curso de su enfermedad. Cinco de ellos eran miembros de una misma colonia. Ellos representan el primer hallazgo de este tipo de asociación. Los estudios clínicos e histopatológicos mostraron la evolución habitual de cada enfermedad. Nosotros creemos que un material fibrohyalino encontrado en secciones histológicas puede corresponder a para-amyloide.

Un hecho notable es que en todos casos el linfoma maligno apareció muchos años después del comienzo aparente de la lepra, lo cual varió de 10 a 22 años.

Se sugiere que esta asociación puede ser frecuente y que todas las adenopatías que se encuentren en los enfermos deben ser investigadas.

RÉSUMÉ

Six malades atteints de lèpre ont développé des lymphomes malins au cours de l'évolution de leur maladie. Cinq d'entre eux étaient membres de la même colonie. Ils représentent la première observation de ce type d'association. Les études cliniques et histopathologiques ont montré que chaque maladie avait suivie son évolution habituelle. Les auteurs croient qu'un matériel fibrohyalin trouvé dans les coupes histologiques peut correspondre à de la para-amyloïde.

Un fait remarquable est que, chez tous ces cas, le lymphome malin est apparu de nombreuses années après l'époque apparente d'éclosion de la lèpre, qui variait de 10 à 22 ans.

On suggère que cette association pourrait être fréquente, et que toutes les adénopathies observées chez les malades de la lèpre devraient être étudiées.

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