Malignant Lymphomas in Leprosy Patients
A Clinical and Histopathologic Study

Eduardo Rodriguez, Yolanda P. de Bonaparte, Marcos C. Morgenfeld
and Rómulo L. Cabrini

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 (2, 3, 8, 9, 14).

Boët (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 I (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, neuralgia of the ulnar nerve, and menopausal amenorrhea.
1954. Erysipelas reaction of the feet.
1956. Reactions of skin and eyes. Bacilloscopy negative since 1957. No nodes palpable on internment, with the exception of those in the inguino-crural 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.
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. 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.

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. Macronodular 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 microoedematosities.

1960. January: Feverish lepromus reaction. Enlarged lymphnodes, generalized patches and mases. Aphonia. Intensive treatment started with sulfones, which was followed by great improvement. November: Patient had increased 12 kgs. in weight.


1963. July: Enormous tumors in the right abdominal-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. 2. The same case with greater magnification. Area with signs of hyalinization.
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.
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.


1945. Probable onset of leprosy.

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Histopathologic report. Macrocopic: 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. Macrocopic: Moderate enlargement of the gland. On cutting, the parenchyma was found to show slight lipomatous impregnation, and soft consisten-<ref><p>Fig. 6. The same specimen stained by Del Rio Hortega's silver technique.</p></ref>
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.


1948. Onset of leprosy.

1951. 40 years old. Interned, suffering from neural cutaneous 11 type leprosy with positive bacilloscopy, disseminated macules and hypochromic scars on the trunk.

1955. 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.


Histopathologic report. Macrosopic: 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 Chlorambucil. 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 lepromatous patients, especially in its lepromatous form (*t*). Lymph nodes are palpable even in patients whose disease is quiescent (*t*). Lymphocytic and plasmacyte hyperplasia are habitually found (*t*). 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 (*t*). 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 tuberculoid 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 (2), 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 adenopaties found in leprosy patients should be investigated.

REFERENCES

8. Mitsuda, K. and Okawa, M. A study of one hundred and fifty autopsies in cases...