ACTA MEDICA IRANICA
Vol. XI; 1968, P. 35-62

A Survey of Malignant Lymphoid Tumors Among Iranians

By

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The following report will present the frequency, histopathologic aspects and clinical features of malignant tumors of lymphoid tissues among Iranians as determined by biopsies and autopsies over a twenty-five years period in the Department of Pathology at Teheran University, which through the seven University affiliated hospitals draws its clinical material from all parts of Iran. All specimens have been reviewed by the author himself. Attention has been drawn to the initial manifestations of these tumors, with special emphasis on the unusual aspects of such initial manifestations.

Selection of Cases

Lymphoid tissue disorders seem to be common among Iranians. TABLE I. shows that among 68,000 biopsies there were 5,814 (8 per cent) lymphnodes examined. These included 1,368 cases of lymphoid tumors, 2,335 cases of tuberculosis and 2.111 cases of metastatic, specific and non specific lesions.

In 1917 performed autopsies, there were 366 cases of malignant tumors, including 81 cases of lymphoid tumors as shown in TABTE 2.

This report does not include the cases of leukemia. All lymphadenopathies have been classified into two main grops: (69,78): 1. Reactionary and inflammatory lymphadenopathies; and 2. Lymphoid tumors.

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The inflammatory and reactionary lymphadenopathies, which will not be discussed in this report, included local lymphadenopathies, specially tuberculosis (40% of all total biopsied Lymph nodes) (1) and generalized lymphadenopathies such as typhoid fever and infectious mononucleosis. Rarely an inflammatory lymphadenopathy was initially misinterpreted as neoplastic. But later demonstrated to be benign.

In this report the author intends only the lymphoid tumors, based on histological aspect of 1368 biopsied cases and 81 autopsies. This group included: 1. Sarcomatous proliferation, 2. Hodgkin's Disease, and other related simple lymphoreticular hyperplasias. In several of the cases multiple and repeated biopsies as well as autopsy have been performed. TABLE 3.

On initial biopsies, a large number of histopathologic subgroups were diagnosed. However, in subsequent biopsies and after autopsies these subgroups merged into a few types, which seemed to have shown different degrees of differenciation at different stages in the evolution of the disease process. This particular consideration has become especially important in recent years because the patients are refered for biopsy examination at an earlier stage, and often at the first indication of lymphadenopathies diagnosed as simple lympho-reticular hyperplasia on first biopsy have with the passage of time acquired the histologic characteristics of malignant disorders.

I. Sarcomatous Proliferation

In our series there were 828 cases (60.5%) of sarcomatous proliferation, diagnosed on first biopsy.

The age range extended from 2 years to 75 years, and the greatest number of patients was seen during the third decade of life. In our series lymphosarcoma occured more frequently in the males, with a male to female ratio of 2.5:1.

Pathology: The designations and classifications proposed for lymphoid tumors seem to be much greater in number than those proposed for tumors of all other tisssues. (38, 44, 56, 57, 80, 91, 94) Although there have been many investigatigations about the different aspects of the lymphoid tumors, we are still for the most part ignorant of the nature and behaviour of the disease process in those cases where these seems to be no correlation

between the histological aspects and the clinical features. The ability and capacity of cellular proliferation and transformation which seems to be the most significant characteristic of malignant tumors is part of the essential physiological function of the reticulo - endothelial system, this system having originated from mesenchymal tissue.

The histological diagnosis of malignant lymphoma is based on: 1. Cytologic abnormality, 2. Presence of infiltration, 3. Stromal destruction and 4. Presence of metastasis in lymphatic and blood vessels.

It should be kept in mind, that proliferation is not uncommon in inflammatory conditions, and can be seen in the tissues surrounding the lymph-nodes. What is of significance in malignant tumors of lymphoid tissues is the capsular destruction and presence of large immature cells in and around the lymphoid tissue. These cells were previously known as endothelial cells; but today they are recognized as reticular cells. (73,78)

In histological studies of this kind of disorder the reticulin should be investigated in the involved tissues. The more mature the tumor cells resembling Lymphocytes, the less the amount of reticulin in the involved tissues. The morphologic characteristics of the tumor cells may remain the same throughout the disease process, or with time may evolve into other patterns. For this reason it often becomes difficult to recommend therapy or predict prognosis of the disease. There are many cases that inspite of histological similarity have a different clinical course, and respond differently to therapy. Some investigators believe that the pathologic findings are constant and the histologic appearance rarely ever change. However, in those where repeated biopsies were performed, the change and evolution of the morphologic patterns could clearly be seen. In some cases even simultaneous biopsies from multiple sites showed different stages and aspects of the disease process in the same person. The following criteria should be observed in the histopathological evaluation of lymphoid tissues:

1. Reactionary and progressive proliferation must be differentiated from sarcomatous proliferation.
2. The proliferation of the follicles, sinuses and medulla should be differentiated from each other.

3. The existing cells are of mesenchymal origin and therefore polipotential. The histological aspects consequently may change on repeated biopsies and the histopathological features of the biopsies differ from that of the autopsy.

The majority of investigators have tried to classify lymphosarcoma histologically. However, it would be better to correlate the histological findings to clinical behaviour. (43) The prognosis of the disease depends on the patient's age. Treatment of lymphosarcoma in children seems to be more successfull than in adults, and its prognosis better than that of the other childhood malignancies. (7) Generally, in sarcomatous lymphoid tumors the normal lymph node architecture is destroyed, sinuses and follicles disappear, and reticular tissue proliferate and replace the normal tissues. To differentiate the different types of lymphoid tumors the existing tumor cells should be evaluated. The essential characteristic of lymphoproliferative desorders is generalized lymphnode involvement such as peripheral, pelvic and periaortic lymph node enlargement, and involvement of extra nodal tissues and spleen. The involved lymph nodes become firm and vary in color. Rarely their surrounding tissue may show inflammatory reactions, and occasionally focal necrosis may be seen. If the capsul is involved, the lesion must be diagnosed as a malignant proliferation In the giant follicular lymphomas the lymph node and the capsul appears to be intact. In lymphosarcomas and reticulum cell sarcoma the malignant cells invade the capsul and involve the surrounding tissues. The enlarged nodes fuse together and bring pressure upon the viscera, arteries of adjacent tissues. In lymphosarcoma and reticulum cell sarcoma the follicular structure is destroyed and the proliferating cells fill the sinuses.

In diffuse small cell lymphosarcoma the preponderant cells are tymphocytes, varying in their degree of maturity. Histologically it is difficult to differentiate leukemia from lymphosarcoma, and the pathologist should be informed if there are any abnormalities in the peripheral blood. (73) In reticulum cell sarcoma the existing cells are irregular, larger than lymphocyte, and containing more cytoplasm. Occasional phagocytic cells are seen which are thought to be non-neoplastic reactive cells. (23) The reticulin appears to be abundant. When the neoplastic cells are closely arranged, the disease could be mistaken with anaplastic carcinoma, or achromic melanoma.

Lymphosarcoma usually occurs in our series in the third to fourth decades of life. In children it occurs more frequently in the male than in the female. But in the advanced age group the ratio of males to be about equal. In our series all of the lymphosarcomas are histologically devided into five groups:

1. Reticulum cell sarcoma.
2. Reticulo-lympho-sarcoma.
3. Lymphoblastic lymphosarcoma.
4. Lymphocytie lymphosarcoma.
5. Giant follicular lymphoma.

Reticulum cell Sarcoma: The existing cells in these sarcomas are of primitive large mesenchymal type. Mallory and Gall (29,75,78) have divided reticulum cell sarcoma into reticulum cell sarcoma with stem cells and reticulum cell sarcoma with clasmatocyte cells. However, usually these two types of disorders appear clinically and histologically to be the same, and in the majority of cases the disease is classified under general difinitions such as reticulum cell sarcoma. Generally the cells are immature, containing irregular and indented nucled nuclei with coarse or dispersed chromatin. In the more anaplastic forms the nucleoli are are distinct. (80) In some cases the cytoplasm may be basophilic. Although there are many cells with large or double nuclei, typical Sternberg cells are not seen. This form usually shows no change on repeated biopsies and autopsy. There were 225 cases in this group, which included 150 males and 75 females; and the ratio of male to female was 2:1. The average age at the time of diagnosis was between 35 and 45 years.

Reticulo-Lymphosarcoma: Of the total of 162 cases in this group 127 were males, and 35 were females, with a male to female ratio of 3.6:1, and the average age at the time or diagnosis was between 35 and 45 years.

Lymphoblastic Lymphosarcoma: Of the 130 cases, 98 were males and 36 were females, with a male to female ratio of 2.6:1. The average age at the time of diagnosis was between 35 and 45 years.

Lymphocytic Lymphosarcoma: There were 262 cases in this group including 190 males and 72 females, with a male to fomale ratio of 2.5:1. The average age at the time of diagnosis was between 35-45 years.

Giant Follicular Lymphoma: There were 49 cases in this group including 32 males and 17 females with male to female ratio of 2:1. The average age at the time of diagnosis was between 25-35 years.

Clinical Considerations: The first manifestations of lymphosarcoma may resemble those of other malignant tumorsor infectious diseases. TABLE 4 shows the incidence of the usual (nodal) compared to the unusual (extra - nodal) clinical manifestation. Of 828 cases there were 668 cases with usual initial manifestations, 150 cases with unusual or extra nodal initial manifestation, and 10 cases with systemic manifestations. The cases in last group were diagnosed only after exploratory laparatomy. In those patients who were less than 10 yearr old, almost one third were suffering from intra-abdominal lymphosarcoma. It should be remembered that in the majority of patients suffering from bone involvement or intra-abdominal tumors pain was the early and initial complaint.

The Usual Maifestation of Lymphosarcoma: TABLE 5 shows the usual initial manifestations. In the 668 nodal manifestations (80,7% of all the patients), the cervical nodes were involved in 559 cases, the axillary nodes in 19 cases, the inguinal node in 15 cases, and the intra-abdominal nodes in 69 cases.

The lymphadenopathy is initially discrete and shows a firm consistancy. With the evolution of the disease process the lymph nodes become larger and form a distinct tumoral mass. In the majority of the cases the skin covering the tumor mass appears to be uninvolved. Although the lymphadenopathy is usually asymetric, symetrical cases are not uncommon. In our autopsies, it has been shown that ascites and pleural effusion caused by the lymphadenopathy is not uncommon. However, no evidence of chylous ascites was noted. In 48 patients with lymphosarcoma who were autopsied, 26 cases showed peripheral node involvement, 11 cases showed intra-abdominal, 6 cases intrathoracic and 5 cases showed both deep and peripheral node involvement. In generalized lymphosarcoma the intrathoracic nodes are often involved and the patologic and clinical manifestations may be directly or indirectly related to the intrathoracic tumor masses. In the lymphosarcomas the patient's resistance declines and he may succumb to secondary infections. The abscess formation that we usually encounter in the lymphosarcoma is caused by secondary

infections; whereas in Hodgkin's disease it is part of the histologic pattern of the disorder itself. Intra-bronchial lymphosarcoma is not uncommon and it may occasionally cause hemoptesis. Tuberculosis usually accompanies Hodgkin's disease, and rarely it may be seen together with lymphosarcoma.

Unusual Initial Manifestation of Lymphosarcoma: TABLE 6 shows the frequency and different localisation of the unusual initial manifestation of lymphosarcoma.

This TABLE shows that next to the lymph nodes, lymphosarcoma most commonly makes its initial manifestation in the skin, bone, small intestine and the tonsils.

Skin: The cutaneous manifestations of lymphosarcoma can be seen as part of generalized lymphosarcoma, or generalized lymphosarcoma, or they may appear as an initial finding. (19,22,87) The cutaneous lesions occur as purplish infiltrates having the appearance of raised irregular plaques with firm consistancy, or as distinct nodules varying in size. The individual plaques may have separate boundaries or they may merge into one another.

The lesione usually involve the deeper layers of the skin, and rarely cause superficial ulcerations. (22, 90) Histologically the middle and deeper part of the dermis and hypodermis is infiltrated by histiocytes, monocytes, plasmocytes, and distorted monocytic cells. When cutaneous lymphosarcoma is diagnosed the patient should be carefully and thoroughly investigated for presence of other manifestation. In addition to the cutaneous lesions directly related to the lymphosarcomatous process, there are other non-specific cutaneous manifestations seen in lymphosarcoma, such as furonculosis, herpes simplex, herpes zoster, and maculopapullar eruptions. Cutaneous lesions are much more common in the lymphocytic lymphosarcoma than the other types.

Bone: Of 828 cases of lymphoid tumors, in 28 cases reticulosarcoma of the bone was the initial manifestation of the disease. TABLE 7 shows the sex incidence and the different bone localisation of this lesion. The age range was 2-63 years, and the average age was 10-20 years. The differentiation of primary reticulo-sarcoma of the bone, from metastatic involvement of the bone by the tumor is very difficult, (28) and

final confirmation can be obtained only at the time of autopsy. Bone reticulum cell sarcoma metastasizes less frequently than reticulo-sarcoma, the femur, pelvis and scapula were more commonly involved than any other bone. However, in the generalized lymphosarcoma the spine is often involved. The bone lesions of reticulo-sarcoma are usually osteolytic in type, whereas in Hodgkin's disease the bone lesions are osteoblastic.

Head and Neck: In our series 50 cases of extra nodal lymphosarcoma were localized in the head and neck. In the lymphosarcoma of the head and neck, the involved organs are in decending order of frequency: the tonsils, the eye and its appendages, the parotid glands, the tongue, the intra- cranial tissues, the submaxillary salivary glands, the maxillary bones and the thyroid. Generally, it has been shown that the incidence of lymphosarcoma of the tonsils and nasopharynx is higher than Hudgkin's involvement of these organs, and it is often misdiagnosed as an infectious process. Lymphosarcoma of submaxillary salivaryglands seens to be rare. (39,77) In our series there were three cases of primary lymphosarcoma of submaxillary salivary glands, and two case of primary lymphosarcoma were males with the ages of 10,19 and 22 years. In the two cases where the lymphosarcoma was localized in the maxillary bones, one was a white 7 years old boy and the other a white 8 years old girl. In both cases the initial manifestation of the disease on admission was maxillary swelling and exophtalmus without and distinct peripheral lymphadenopathy; and in both cases irregular tumor masses could be palpated on abdominal examination. The autopsy findings of the eight years old girl showed enlargement and tumor infiltration of the right cheek and upper eye lid. The ovaries were large, both together weighing 690 gm. Microscopically the tumor appeared to be composed of mononuclear cells ressembling lymphocyte, immature reticulum cells, and a few dispersed pale histiocytes having the appearance of starry sky cells as described in Burkitt's lymphoma. (13,14,15,35,66,68,96,97.)

Tonsils: In our series of the total of 14 cases, 11 were males, and 3 females, with a ratio of approximatly 4 males to each female. The peak frequency was during the fourth decade of life. The prognosis of tonsillar lymphosarcoma seems to be better than other malignancies of the tonsils.

Eye : Lymphosarcoma of the eye and its appendages is not uncommon, since it contains tissues of reticulo-endothelial origin. (6, 26, 60) It is not unusual for the ophtalmologist to make the initial diagnosis of systemic lymphosarcoma. In our 14 cases the initial manifestations of lymphosarcoma were in the retrobulbar area (4 cases) in the choroid and tarse (6 cases) and in the conjonctivae (4 cases).

Thyroid: Lymphosarcoma of the thyroid gland appears to be rare. (63, 64, 79) It usually originates in those areas of the gland where lymphoid hyperplasia is found. Tumor of the thyroid gland was the initial manifestation of lymphosarcoma in one of our 828 cases. The patient was a middle aged white woman.

Gastrointestinal tract: As has been suggested by Kundart as early as 1893 and later by many other (33, 46, 50, 92), lymphosarcoma apart from involvement of the lymph nodes may involve the digestive tract in a diffuse manner. It is most difficult to determine whether such involvement of the digestive tract is part of a systemic spread of the disease, or represents its initial manifestations. (5, 75) It can generally be said that malignant lymphomas of gastrointestinal tract have not as yet received the attention they deserve. There are still many diagnostic difficulties in its clinical, pathological, and radiological features. The lesion shows a great tendency to perforation. In our series, of the total of 828 cases, 36 cases (4%) were gastrointestinal lymphosarcoma; involving the stomach in 2 cases, the small intestin in 18 cases, the sigmoid and coecum in 6 cases and the rectum in 4 cases. The diagnosis of all of these cases was based on operative findings and no other organ involvement could be detected. In our series lymphosarcoma of the intestines was more common in children than in adults, whereas our two cases of lymphosarcoma of the stomach were both adults. Malignant lymphoma of the gastro-intestinal tract may manifest itself as multiple pedonculated or secile polypous tumors. (16) The majority of patients have initially an intestinal disorder and not a systemic lesion. However, it should be kept in mind that such lesions rarely ever remains localized throughout the evolution of the disease. The lesion may be localized in the mucosa or submucosa, and causes thickening of the intestinal wall.

Stomach: Lymphosarcoma makes up about 3% of all malignant

tumors of the stomach. (5, 16, 25, 37, 45, 65, 81, 93) It usually involves the mucosa and submucosa, but does not invade the muscular coat and therefore does not produce peri-gastric sclerosis. The patient suffering from gastric lympho-sarcoma may complain of periodical perigastric cramps for many years, resembling the symptoms of peptic ulcers. In this stage if the stomach is examined carefully no gross abnormality may be observed in the mucosal layer and only on histological examination can a diffuse infiltration of abnormal and mitotic lymphocytes be seen. This period of the disease is called the mucosal lymphosarcoma phase. If the patient is operated in this phase, he will have at least a 5 years survival chance; whereas without operation the gastric wall becomes progressively more involved, leading to ulceration of the mucosa and reaching a stage where diagnosis is not difficult. Generally these patients are younger than the patients with gastric epithelioma. (62, 76) Histologically gastric lymphosarcoma may appear as reticulum cell sarcoma, lymphocytic lymphosarcoma or gastric lympho-reticulosis. (41)

Small Intestine: Lymphosarcoma of the small intestine is very rare. (51, 71) Any part of the intestine can be involved, but the ileum appears to be more commonly affected. It is rarely ever diagnosed before operation. Lymphosarcoma of small intestine is usually multifocal appearing as an unnular tumor, but rarely causing constriction. There is only minimal fibrous reaction around these tumors and hence perforation is not uncommon. Histologically there may be two different forms: lymphosarcoma with small cells and lymphosarcoma with reticular cell. (17, 71)

Rectum: Lymphosarcoma of the rectum appears to be less frequent than that of the other parts of the gastro-intestinal tract. In our series there were only 4 cases. It usually appears localized, and rarely ever manifests itself as a diffuse lesion. One of its clinical characteristics is the absence of spasm and irritability. 52 Benign lymphoma of rectum has been reported, and it should be differentiated from malignant lymphoma. (17,34) Malignant lymphoma of the rectum usually appears as a circumscribed small pedonculated or secile tumor, having originated from the lymphoid tissues of the rectum.

The other unusual initial manifestations of lymphosarcoma studied in our serie were: in the breast (2cases), involving the urinary bladder (one case), the testis (one case) and the ovaries (one case). Malignant lymphoma of the urinary bladder according to the literature is more frequently seen in the female, and the patients are evenly distributed in the fourth decade of life. (9) Its clinical characteristics are periodic hematuria and dysuria. The tumor is usually a pinkish round smooth firm nodule. The covering mucosa is usually not involved, but sometimes it may be ulcerated. The tumor is originally located in the lamina propria, but later may involve the superficial and muscular layers, and may rarely invade the surrounding tissues of the urinary bladder. The neoplastic cells are of lymphocytic and reticular type.

Testis: Although in a generalized and disseminated lymphosarcoma the testis may rarely be involved, (88) in our series there was only one case. The patient was a 25 years old man, with the clinical symptoms of fever and painful testicular enlargement. The autopsy of this patient showed involvement of other organs including brain and skull.

Heart and Pericardium: Lymphosarcoma involving the heart and pericardium is usually not diagnosed clinically. (59) In our series lymphosarcoma of these organs was diagnosed only at the time of autopsy, and these cases have therefor not been included in TABLE 6 showing the initial unusual manifestation. Of 48 cases that came to autopsy 5 showed myocardial infiltration by lymphosarcoma.

Lung: Lymphosarcoma of the lung progresses slowly and the incidence seems to be the same for males and females. The majority of the patients may have no symptoms or they may complain of cough or hemoptesis. (40) The lung, like other organs may be involved initially. In such cases the lesion manifests itself as a solitary and nodular tumor which can be removed surgically with a fairly good prognosis. (49,70,74) The tumor is white or pale yellow, it may invade its surrouding pulmonary tissues, or it may have a distinct boundary separating it from its surrounding tissues. The tumor is usually localized in the peribronchial areas, and histologically composed of lymphoblasts, lymphocytes, and reticular cells. Generally it can be said, that if the lesion is initially located in

the lung, the patient will have a 5 years survival. However, with the generalized form of the disease, showing a milliary infiltration of the lung, the prognosis seems to be poor.

II. Hodgkin's Disease

In our serie of 5814 lymph node biopsies and 1917 autopsies, there were 540 and 29 cases of Hodgkin's rispectively. Of the 540 cases of Hodgkin's disease proven by biopsy 425 (78%) were males and 115 (22%) females. Of the 29 autopsied cases of Hodgkin's disease there were 24 males, and 5 females. The average age of the patients at the time of diagnosis was between 25 and 35 years. (3,10,12) (TABLES 8 and 9).

The histological characteristics of Hodgkin's disease, descaibed by different investigators and schools are based on two essential criteria: 1. Ability of cell proliferation and 2. Ability of cell transformation. These characteristics are not only of diagnostic importance in the affected tissues of the patient, but they could be of significant value in tissue cultures of the patient's lymph-nodes as well. (2,4) It can therefore be said that in Hodgkin's disease par excellance the degree and extent of cell proliferation and transformation bears a direct relationship to the malignancy of the tissue involved. The proliferative activity described in Hodgkin's disorder can be simple, with cells remaining their normal morphlogie characteristics, or it may be accompanied by change and transformation of the original cells into new cell types, with abnormal shape and size differing conspicuously form their ancestral cells. The second type of proliferation could be named transforming proliferation.

1. Simple Proliferation: As is well known all reticulo - endothelial tissues are composed of parenchyma and stroma, both of which having a remarkable proliferative activity, can proliferate separately or together. This characteristic is retained even in the pathologic disorders of the reticulo-endothelial tissues. For this reason the pathological proliferation can be divided into 3 subgroups: 1. Simple lymphoid proliferation, 2. Simple reticular proliferation and 3. Simple lympho - reticular proliferation. TABLE 10.

Simple Lymphoid Proliferation: Of 540 total cases there were 27 cases (5%) diagnosed on initial biopsy as simple lymphoid hyperplasia, or Hodgkin's disease in its early phase of evolution. (11,95) In this type

of proliferation the lymphocytes proliferated diffusely, and lymphoid follicles were enlarged and clear. In the majority of these cases lymphadenopathy (unilateral or bilateral) was limited to the neck. Of these 27 cases only seven (25.9%) returned (within 8-24 months) for follow-up studies; and of these seven one expired and has been autopsied showing generalized Hodgkin's disease, two showed Hodgkin's disease on repeat biopsy, and 4 showed again the simple lymphoid proliferation seen on initial biopsy. This form could be mistaken with inflammatory or irritative disorders. However, there are several criteria for separating the simple lymphoid hyperplasia from irritation or inflammatory reactions. In the inflammatory conditions the evisting cells are usually well differentiated, and there are many macrophages in the involved lymph nodes; whereas in the simple lymphoid proliferation the cells are not well differentiated and no macrophages are seen. In all of these cases the histological appearance alone may be sufficient for diagnosis but should be judged together with the clinical and radiological findings. (55,72) Occasionally repeat biopsy may be required.

Simple Reticular Proliferation: Of 540 cases there were 28 cases (5.1%) diagnosed on initial biopsy as simple reticular proliferation. The involved lymphoid tissues were grossly smooth, and sticky becase of the presence of intestinal juices. (3) Histologically the existing cells showed large ovoid nuclei with fine chromatin structure; Mitotic cells were present in the involved tissues. In this form proliferation and elongation of the endothelial lining cells of the lymph and blood vessels of lymph nodes are conspicuous and should be looked for. In the majority of these cases the bone marrow showed a reticular proliferation.

Simple Lympho-Reticular Hyperplasia: Of the total of 540 cases, there were 18 (3.5%) cases which showed reticular proliferation together with lymphoid proliferation. The lesion manifested a nodular or diffuse pattern, often obscuring structure and rendering recognition of the sinuses and follicles was difficult. Focal necrosis seemed to be striking in this disorder. The histiocytes, and reticulum cells were swollen, and vesicular. Epithelioid cells were seen despersed among the necrotic cells.

2. Transforming Proliferation: In this type of proliferation some of the proliferated cells retain their normal morphological features while

others are transformed into new abnormal cells. It is for this reason that the involved tissues usually show a pleomorphic pattern. The existing cells are of different shapesand sizes, and include lymphocytes, plasma cells, eosinophils, pre-Sternberg and Sternberg cells. Some of the cells are in various stages of mitosis. Of 540 total cases 467 showed trans-forming proliferation, presenting the following forms:

Sarcomatous Proliferation: Although many investigators believe this form to be rare, it occured in 73 of our cases with an incidence of 13.4%. The existing reticulum cells in this type show ill-defined boundaries, basophilic cytoplasm and large nuclei. The majority of the existing cells are undifferentiated. Dispersed among these, a few lymphoblaste and myeloid cells may be seen. In some areas, specially around the sinuses, the typical pleomorphic pattern is striking.

Tuberculoid Proliferation: In 12 of the 467 cases of transforming proliferation, the histological picture of the lymph node showed inters-persed among the normal and abnormal reticulum cells and lymphocyte, round or ovoidal cells with eosinophilic cytoplasm forming small clusters resembling pseudo-follicles. In some of these pseudo-follicles the described cells fuse to each other and form giant cells. These giant cells seem to disappear on tissue culture of patient's lymph node, and could not be followed.

Inflammatoid Proliferation: The tissue changes observed in this type of proliferation resemble those of an inflammatory process. Some of these cases were not diagnosed on initial biopsy. However on subsequent biopsies and on autopsy the disease was confirmed. In these forms the sinuses appear to be dilated, while the reticular fibers become dense, surrounding more or less differentiated reticulum cells and polymorpho-nuclear leucocytes.

Sclerosing Proliferation: It is well known that sclerosis is a usual finding in the malignant lympho-granulomatous tissues, and can be found in greater or lesser amounts in all cases. (47) However it appears as a particularly significant feature of the sclerosing type of proliferation. Our experience also has shown that when this type of proliferation is seen, irrespective of the site of biopsy, the mediastinal lymph nodes are always affected as well. Histologically the collagen fibers become hypertrophied in the early phases. Later the fibrillary reticulin become thickened and

the histiocytes lose their stellate shape and convert into fibroblast cells. In this later stage interstitial juices are present and the collagen fibers stains paler than normal. Sometimes the sclerous extensions migrate from the peripheral zone to the center and merge together, forming an irregular network containing normal and abnormal reticulum cells, lymphocyte, and others atypical or abnormal cells as described above.

Necrotic Proliferation: Generally, all the cells in malignant lympho-granulomatous tissue are active. If a few of the cells become necrotic as a result of pressure from the above described encircling sclerous strands, the majority of the cells retains their morphological characteristics. However, in the necrotic proliferation necrosis appears as the outstanding feature of the lesion, and may even at times be mistaken for tuberculous necrosis.

Proliferation Together With Tuberculosis: There are many reports concerning Hodgkin's disease accompanies by tuberculosis. (83) In our series in 4 per cent of the cases these two lesions occured together. In these cases the tuberculous and Hodgkin's lesions were seen in the same groups of involved nodes.

Granulomatous Proliferation With Abnormal Cells: In our series 54.36% of 540 total cases of Hodgkin's disease showed typical granulo-matous Hodgkin. The cells seen are either normal constituent of the lymph node or abnormal cells not usually found in a lymph node. The majority of the latter cells are undifferentiated reticulum cells, abnormal reticulum cells and pre-Sternberg and Sternberg cells.

Unusual Forms of Hodgkin's Disease: Clinical and histopathological aspects of Hodgkin's disease is not always classic as described in the text books. Some times as shown in TABLE 11, it manifest itself in unusual sites not diagnosed clinically, but confirmed only in histopa-thological examination of the lesion. (8,21,24,27,30,31,32,36,42,48,53,54,58, 61,82,84,85,86,89,97.)

Table No. 1

Incidence of Lymph Node Disorders in 5814 Lymph Nodes Studied Among 68000 Biopsies

Total number of biopsies	Lymph nodes examined	Tuberculosis of lymph onde	Malignant lymphoma	All other lesions
68000	5814	2335	1368	2111
		40%	23%	36%

Table No. 2

Incidence of Lymphoid Tumors in 1917 Autopsies

Total number of autopsies	Number of all malignant tumors	Number of malignant lymphoid tumors	
1917	366	81	Hodgkin's disease 29
			Malignant lymphoma 52

Table No. 3

Incidence of Different Types of Lymphoid Tumors

Total number of malignant tumors of lymphoid tissues	Lymphoid tumor and its related lesions	Hodgkin's disease and related disorders
1368	828	540
	60 5%	39.5%

Table No. 4

Different Manifestations of 828 Lymphoid Tumors

	Usual (Nodal)	Unusual (Extra Nodal)	Systemic
Number of cases	668	150	10
Perecent	80.7%	18%	1.3%

Table No. 5

Loealization of the Usual (Nodal) Initial Manifestations of Lymphosarcoma

Site of manifestation	Number of cases
Peripheral lymph nodes:	
- Cervical	559
- Axillary	19
- Inguinal	15
- Generalized	3
Intra thoracic	3
Intra abdominal	69
Total	668

Table No. 6

Localization of the Unusual (Extra-Nodal) Initial Manifestations of Lymphosarcoma

Site of manifestation	Number of case
Skin	31
Bone	28
G. I. Tract:	
- Small Intestin	18
- Cecum & Sigmoid	6
- Liver	6
- Rectum	4
- Stomach	2
Head & Neck:	
- Tonsils	14
- Eye	14
- Parotid glands	7
- Tongue	5
- Intercraniale	4
- Salivary gland	3
- Maxillary bone	2
- Thyroid gland	1
Miscelaneous	5
Total	150

Table No. 7

Sex Incidence and Localisation of 28 Cases of Bone Reticulosarcoma

Femur	5	M	3	Pubis	1	M	-	Sternum	1	M	1	Tibia	2	M	2
		F	2			F	1			F	-			F	-
Pelvis	4	M	3	Sternum	1	M	-	Tibia	2	M	2	Peroneum	2	M	2
		F	1			F	-			F	-			F	-
Scapula	4	M	2	Tibia	2	M	2	Peroneum	2	M	2	Maxillary bone	2	M	2
		F	2			F	-			F	-			F	-
Rib	3	M	3	Peroneum	2	M	2	Maxillary bone	2	M	2	Sacrum	2	M	-
		F	-			F	-			F	-			F	2
Humerus	2	M	2	Maxillary bone	2	M	2	Sacrum	2	M	-	Humerus	2	M	-
		F	-			F	-			F	2			F	-
Sacrum	2	M	-	Humerus	2	M	-	Humerus	2	M	-	Rib	3	M	-
		F	2			F	-			F	-			F	-
Maxillary bone	2	M	2	Rib	3	M	-	Rib	3	M	-	Scapula	4	M	2
		F	-			F	-			F	-			F	2
Peroneum	2	M	2	Scapula	4	M	2	Scapula	4	M	2	Pelvis	4	M	3
		F	-			F	2			F	2			F	1
Tibia	2	M	2	Pelvis	4	M	3	Pelvis	4	M	3	Femur	5	M	3
		F	-			F	1			F	1			F	2

Table No. 8

Sex Incidence in 540 Cases of Hodgkin's Disease

	Male	Female	Total
Number of Cases	425	115	540
Percent	78%	22%	100%

Ratio of Male to Female 3.5:1

Table No. 9

Age Incidence in 540 Cases of Hodgkin's Diseases

Age in years	Up to 15	15-24	25-34	35-44	45-54	55-64	65 & over	Total
Number of cases	38	73	124	121	97	49	38	540
Per cent of Total cases	7%	13.5%	23%	22%	18.5%	9%	7%	100%

Table No. 10

Different Types of Cell Proliferation and Transformation in 540 Cases of Hodgkin't Dis.

	Nmber of cases	Per cent of Total Case
Simple proliferation		
Reticular	28	5.1%
Lymphoid	27	5%
Lympho-reticular	18	3%
Transforming proliferation		
Granulomatous	294	54.36%
Sarcomatous	73	13.36%
Sclerosing	38	7.2%
Necrotic	18	3.5%
Eosinophilic	16	2.9%
Tuberculoid	12	2.2%
Inflammatoid	8	1.5%
With polynuclears cells	7	0.2%
With plasmocytic cells	1	0.8%
Miscelaneous	24	5%

Table No. 11

Unusual Sites of Initial Manifestation of 39 Cases of Hodgkin's Disease Among 540 Cases Studied

Site of manifestation	Number of cases
Abdomen	12
Small Intestin	6
Bone	4
Stomach	3
Mediastinum	2
Eye	2
Spleen	2
Bronchus	1
Pharynx	1
Retropharynx	1
Parotid gland	1
Liver	1
Larynx	1
Thyroid	1
Skin	1
Total	39

Summary

A Survey of Malignant Lymphoid Tumors Among Iranians

The frequency, histopathologic features, and clinical aspects of malignant lymphoid tumors among Iranians are discussed on the basis of 68,000 consecutive biopsies and 1917 autopsies performed over a twenty-five years period in the Department of Pathology at Teheran University. Of the 5814 lymph nodes examined on biopsy, 1368 (23%) showed malignant lymphoid tumors. Among the autopsied cases there were 366 cases of malignant tumors, and of these 81 cases showed malignant lymphoid tumors.

The malignant lymphoid tumors were devided into two major groups of Sarcomatous proliferation and Hodgkin's disease. There were 870 cases of Sarcomatous proliferation, of which 828 cases were diagnosed initially by biopsy. These cases of Reticulumcell-sarcoma, 162 cases of Reticulo-lymphosarcoma, 130 cases of lympho-blartic-lymphosarcoma, 262 cases of lymphocytic lymphosarcoma and 49 cases of Giant follicular lymphoma. These were further analyzed on the basis of age distribution, sex incidence and site of initial manifestation. Nodal involvement was the initial manifestation in 89% of the cases, whereas extra-nodal initial manifestations appeared in 9.5% and systemic manifestations in 1.5% of the cases. There were 569 cases of Hodgkin's disease, of which 540 cases were diagnosed initially by biopsy. The cases of Hodgkin's disease were discussed and devided on the basis of the pattern of simple or mixed cellular proliferation and transformation.

Resumé

La Revue des Lymphomes malins chez les Iraniens.

La Frequence et l'aspect clinique et histologique des lymphomes malins chez les Iraniens est étudiée sur la base de 68,000 prélevements biopsiques et 1917 autopsies, pratiques pendani 25 années de l'activité du Departement d'anatomie Pathologique de l'Universite de Teheran.

Un total de 1368 tumeurs lymphoides sont diagnostiques parmi les quels dans 828 cas la tumeur ganglionnaire était un lymphome malin (Proliferation sarcomateuse). Et dans 546 cas il s'agissent d une lympho-granulomatose maligne.

Ces lymphomes malins sont constitues par 225 cas de reticulosarcome, 162 reticulo-lymphosarcome, 130 lymphosarcome lymphoblastiques, 262 lymphosarcome lymphocytique et 49 cas de lymphome folliculaire geant.

La distribution selon le sex, la localisation anatomique de la lesion initiale et les manifestions nodale, extra nodale ou systemique de cas lesions sont étudiées en detail.

Pour les cas de maladie de Hodgkin la classification est faite selon l'aspect simple et mixte de la proliferation et transformation cellulaire.

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