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Burkitt's Lymphoma*

(Studies of 20 cases seen in Hacettepe Children's Hospital Compared with Burkitt's Tumor in African Children)

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Although reports of malign tumor involving the jaw in African children had been previously published in the literature, it was first described as a distinctive clinical condition and the commonest malignance of African children in 1958 by D. Burkitt.[1, 2] Since then the eponym of "Burkitt's Tumor" has been introduced into medical literature. Following pathological studies of this tumor, it is regarded as a malign lymphoma, Burkitt's type.[2–5] Apart from Africa, numerous cases have been reported from various parts of the world, including Turkey.[6, 21] The characteristic clinical features of Burkitt's Tumor may be summarized as follows:[3,5,22]

1. A rapidly growing solid tumor with a rapidly fatal course, if untreated.

2. Predominantly a tumor of childhood. However, the disease may occur in any age group.

3. Tumors are predominantly extranodal. A jaw tumor with a peculiar pattern of involvement of various viscera and bilateral ovarian tumors is a characteristic feature.

4. Radiology usually shows a translucent osteolytic foci when the tumor in the jaw is clinically noticeable.

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5. Involvement of superficial lymph nodes and the development of leukemia is rare.

The purpose of this article is to study the clinical and pathological aspects of 20 cases of Burkitt's tumor diagnosed in the Department of Pediatric Pathology, Hacettepe University Children's Hospital between 1966 and 1972 and compare them with Burkitt's tumor occuring in African children.

Materials and Methods

Cases were accepted for study when there was histopathological diagnosis of Burkitt's tumor. All materials except for two post-mortem studies were obtained by surgical biopsy. The biopsy material was immediately fixed in buffered 10 % formalin and in Zenker-formalin solutions and embedded in paraffin as a pathological routine. In cases when fresh tissue was available, imprints of the tumor were made and stained with Giemsa, oil-red-O, and PAS (periodic acid-Schiff); sections of paraffin embedded tumor were stained by hematoxylin-eosin, PAS and methly-green-pyronin methods. A tumor was accepted as Burkitt's Tumor when the histopathological and cytological characteristics corresponded to the criteria as documented by various authors.[2, 5, 2, 2] which may be summarized as below:

1. Monotonous overgrowth of lymphoid cells with little variation in size and shape, described as lymphoblasts or immature reticulum cells (Fig. 1). The nucleoli are prominent and are usually 2-5 in number (Fig. 2). The cytoplasm forms a narrow rim which gives amphophilic staining in hematoxylin and eosin stained sections, use of an oil immersion objective will also reveal the cytoplasmic vacuoles that are clearly seen in imprint preparations. (Fig. 3). A high cytoplasmic content of RNA is responsible for pyronophilia when stained with methyl-green-pyronin Y, (Fig. 4). oilred-O will also reveal abundant coarse lipid droplets in tumor cells and in non-neoplastic histiocytes. Although occasional cells may contain PAS positive granules that can be removed by prior digestion with diastase, the majority of the tumor cells show no PAS reaction. Supporting stroma and reticulin fibre is scanty when stained for reticulin fibres.

2. Phagocytic histiocytes are responsible for the characteristic, although not pathognomonic, "starry sky" pattern. (Fig. 5 a, b.) The histopathological criteria as indicated above were present in 20 cases. The patients' charts and autopsy protocols were reviewed. Letters were written to the families in 17 out 920 cases (3 out of 20 died during the operative period) whose conditions were unknown since the discharge from the hospital. All except 3 families responded to the inquiry.

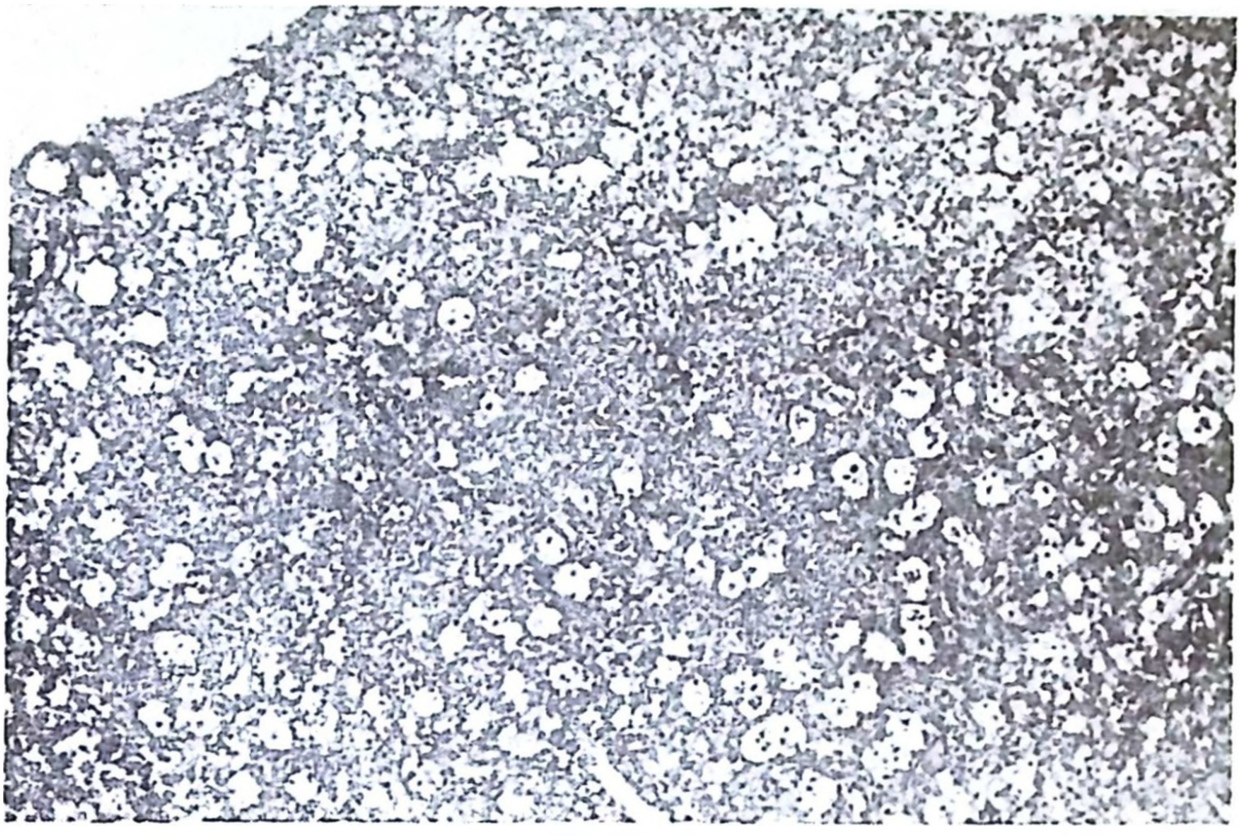


Figure 1
Section of tumor showing monotonous architecture of lymphoid cells. (Hematoxylin and eosin 100 x)

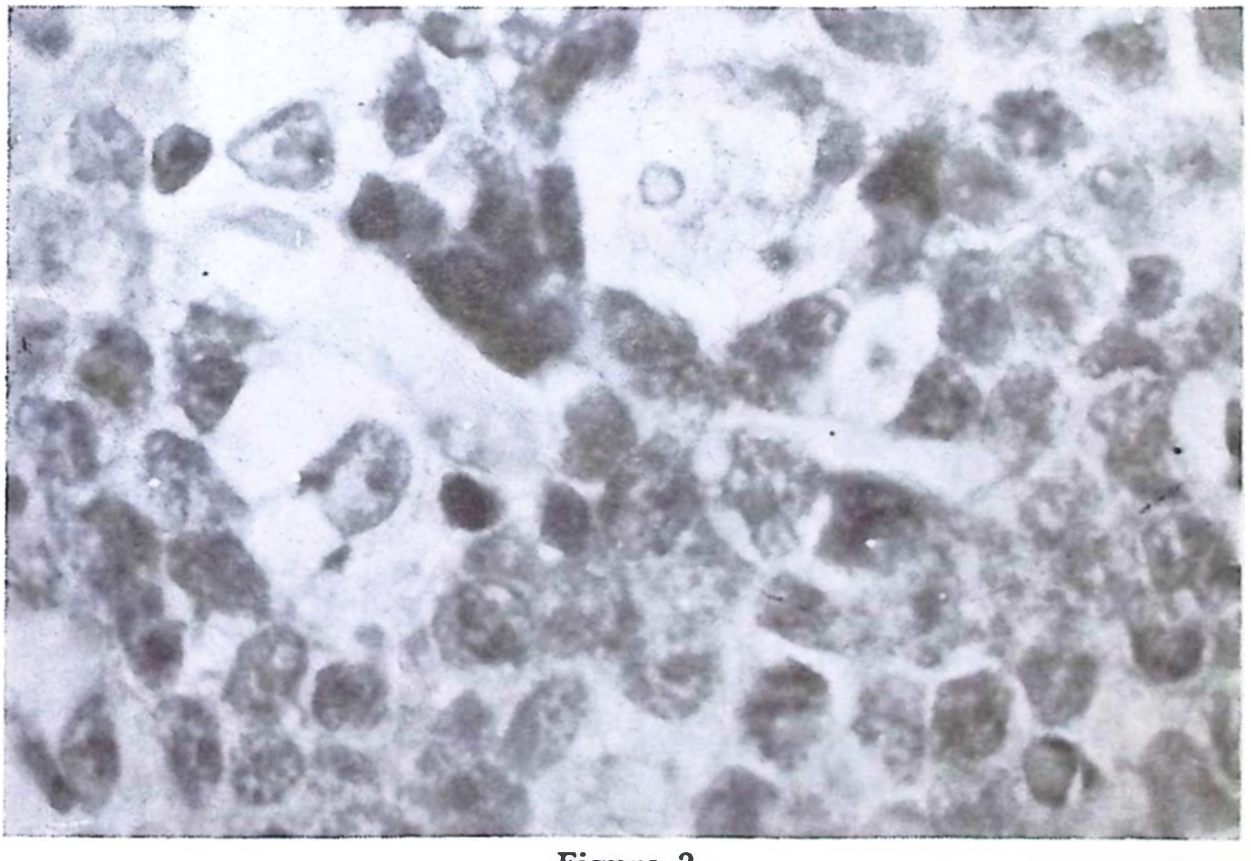


Figure 2
Nucleoli visible under the immersion oil. (Hematoxylin and eosin 950 x)

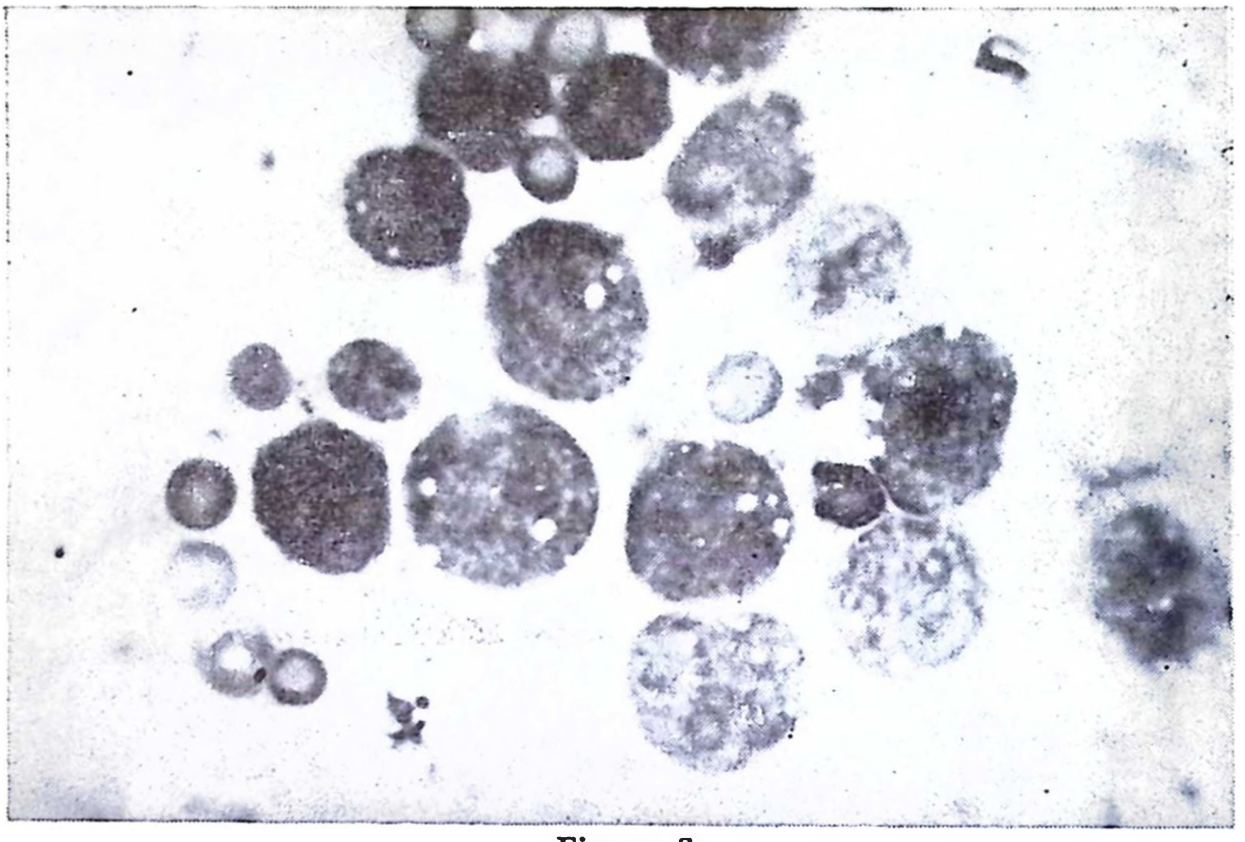


Figure 3
Imprints of tumor unfixed showing vacuoles. (Giemsa 950 x)

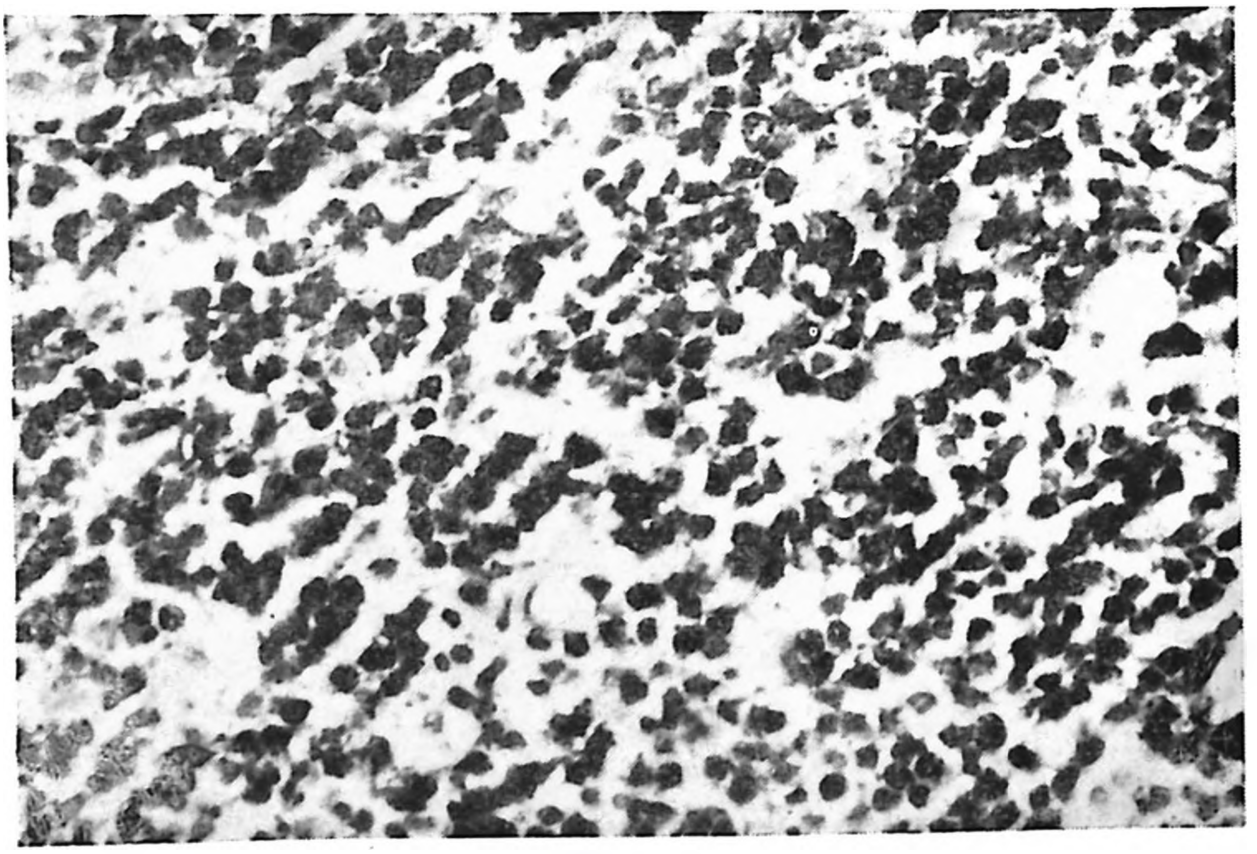


Figure 4
Cytoplasmic pyronophilia of tumor cells. (Methyl green pyronine Y 250 x)

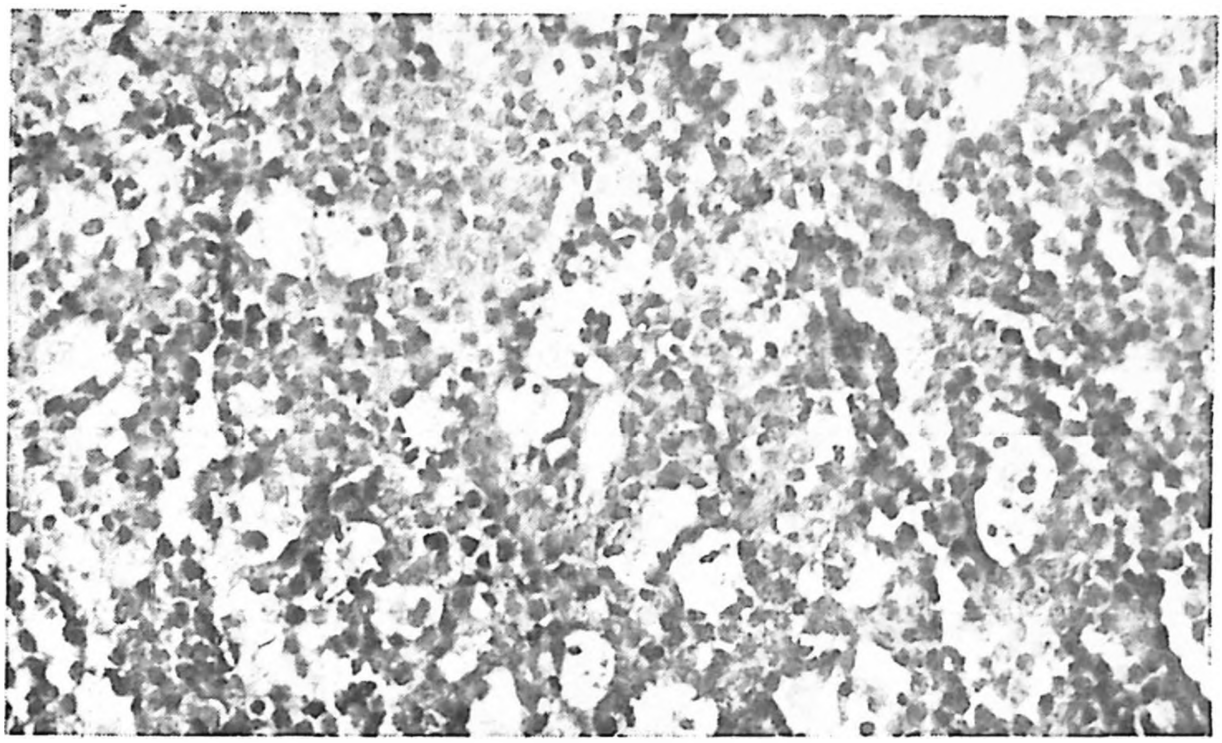
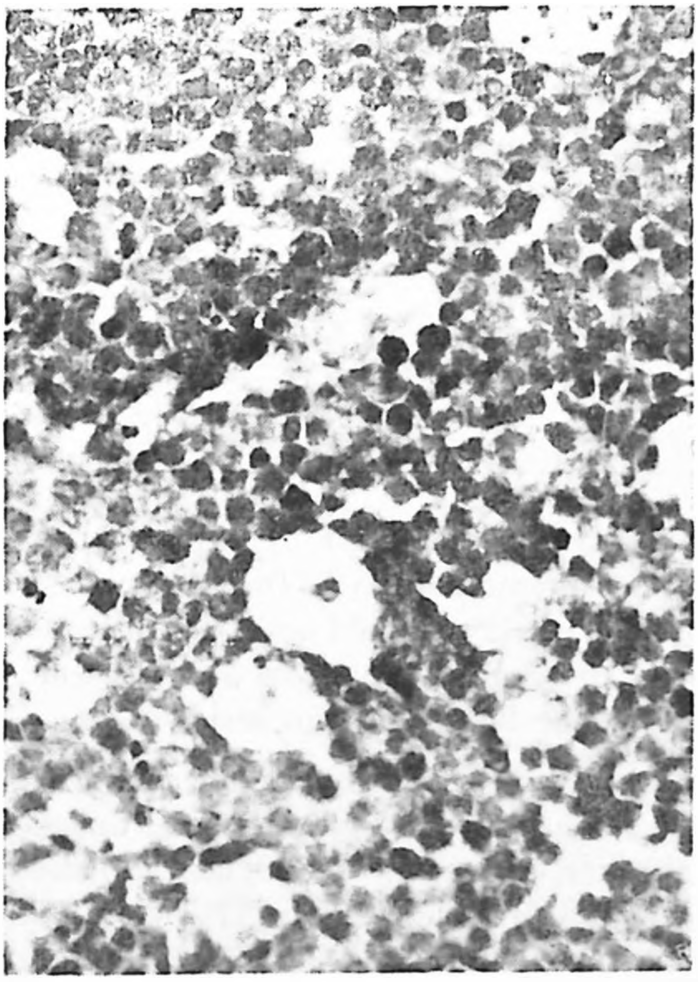


Figure 5 a

Monotonous architecture of tumor showing two types of cell.
a) Phagocytic histiocytes with large pale cytoplasm "Starry Sky" pattern.



Tumor consisting of large lymphocytic cells which are often identified as lympho-
b) blasts or immature reticulum cell. (Hematoxylin and eosin 250 x)

Observations

A summary of the pertinent data for each of the 20 cases is given in Table I.

TABLE I

CLINICAL PRESENTATION AND SITE OF TUMOR DISTRIBUTION SEEN IN 20 CASES

Clinical Presentation and Site of Involvement	Number of Cases, on Admission	Number of Cases, on Following	Total	Percentage of Cases
Jaw Tumor	5	–	5	25
Abdominal Tumor	14	2	16	80
Pleural effusion	3	1	4	20
Cranial Involvement	1	1	2	10
Paraplegia	1	–	1	5
Thyroid	5	–	5	25
Gonad	2	1	3	15
Kidney	3	2	5	25
Skeleton, other than jaw	2	–	2	10
Peripheral lymph nodes	–	1	1	5
Mediastinal lymphadenopathy	2	–	2	10
Mesenteric lymph nodes	13	–	13	65
Retroperitoneal lymph nodes	11	–	11	55
Tumor cells in Bone Marrow	2	–	2	10

Age and sex distribution: 15 out of 20 cases were male. The overall ratio of male to female was 3:1. In the African series this was 2.1:1. The youngest patients was 2 years old and the oldest was 14 years old. The median age at the time of diagnosis was 6.3 years (Table II); this was reported as 6 in the larger African series.

Localization and clinical manifestations of cases: In 14 out of 20 cases the tumor was only in the abdomen, in 4 out of 20 cases the tumor was only in the face, in one case in both face and abdomen and in another in the paravertebral muscles (Table III). More detailed localization of the tumor is shown in Table IV. The main symptom in patients with abdominal tumors was abdominal swelling; in addition, abdominal pain was occasionally recorded. Fatigue, anorexia and weight loss were

TABLE II

AGE AND SEX DISTRIBUTION OF 20 CASES

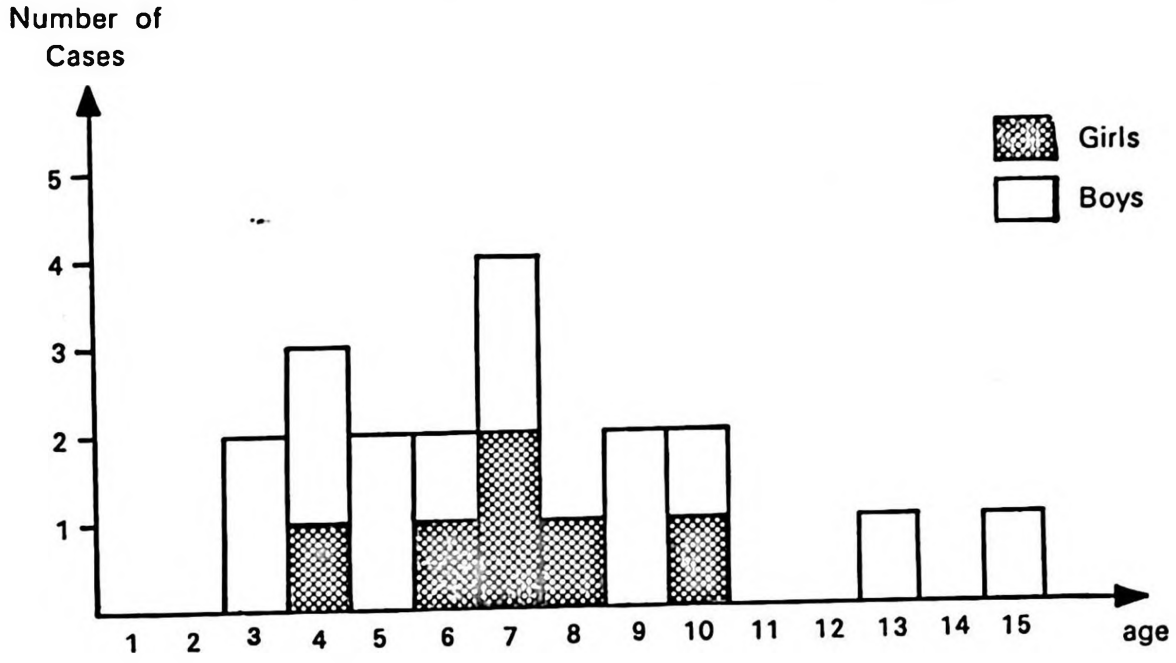


TABLE III

LOCALIZATION OF BURKITT'S TUMOR CASES

Localization	Number of Cases	Percentage
Abdomen	14	70
Jaw	4	20
Abdomen and Jaw	1	5
Lumbar Epidural Space	1	5

TABLE IV

SHOWING REPONSE TO CHEMOTHERAPY

Mode of Administration	Number of Patients	Number of Patients Showing Regression	Number of Living Patients	Died
5–10 mgr/kg Endoxan	9	1	0	9
30–40 mg/kg Endoxan	5	3	3	2

present in about 50 % of the cases. On abdominal examination more than one mass was usually palpated. Pleural effusion was noted in 3 out of 20 patients with abdominal tumors. The central nervous system

was involved in 3 out of 20 cases. In one, the presenting symptom was paraplegia and a biopsy of the tumor was obtained from the paravertebral space. Subsequent myelography revealed a block at the level of L_{4-5}. In the second case, the central nervous system was involved by the extension of the orbital tumor, and in the third, CNS involvement occurred during the follow-up period when cytological examination of cerebrospinal fluid showed tumor cells.

The thyroid gland was involved (Fig. 6) in 5 out of 20 cases. On palpation, the tumors were firm, round and mobile with smooth surfaces.

Abdominal organs; The gonads were involved in 3 out of 20 cases (2 cases ovaries and 1 case testes, see Fig. 7). Kidney (Fig. 8), liver, bowel (Fig. 9), and abdominal lymph node involvement were also common. Except for one case (Case No. 5) no involvement of peripheral lymph nodes was seen. In this series, none of the cases developed leukemia. Only in two cases bone marrow examination revealed vacuolated blast cells.

Although most of the studies for organ distribution of the tumor were made by surgical biopsy, we feel that consideration of the clinical presentation of the tumor may be of value.

Treatment

The treatment of choice for all cases in this series was chemotherapy. This was because it is the most sensitive of all tumors to chemotherapeutic agents and due to the multicentric nature of the tumor. In some cases, in this series radiotherapy was also given. The drug used in the treatment of our cases was endoxan, given intravenously 5 mgm/Kg./body weight once a week or 30 mgm/Kg/body weight once in 3 weeks. According to the drug dosage used, patients were divided into 2 groups (Table V). In the first group there were 9 patients, all of which died 1 to 4.5 months after the diagnosis was made. In one patient in this group with a facial tumor, the tumor receded after treatment, but the patient died a month later with a recurrence of the tumor both on the face and in the abdominal organs.

In the second group there were 5 patients, two of which had abdominal tumors. In spite of therapy they died within 1.5 to 2 months. The other 3 patients responded to therapy with the disappearance of the tumors in 2 cases and tumor regression in the other and they were alive up to the time of the preparation of this manuscript. Two of the 3 living patients had abdominal and the third facial tumors (Fig. 10). After treatment with endoxan, the jaw tumor almost completely regressed (Fig. 11),

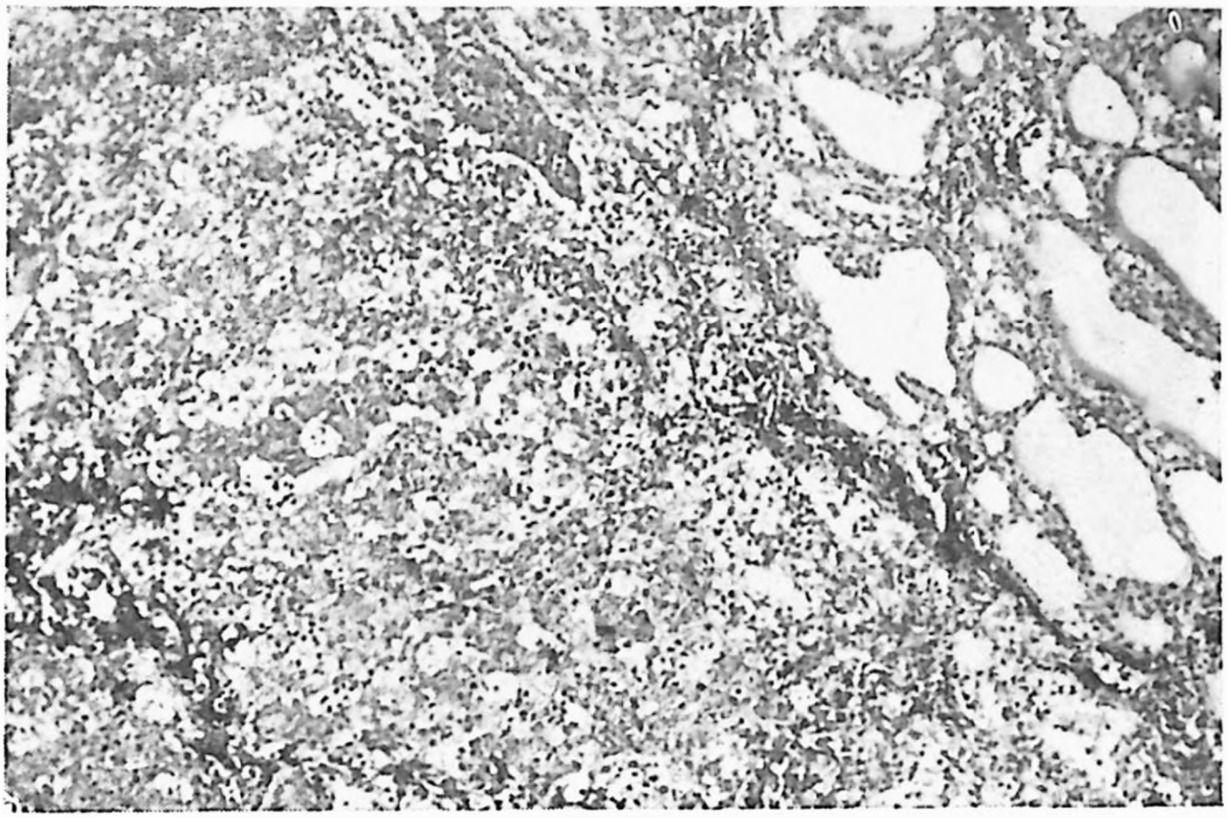


Figure 6
Burkitt's Tumor metastasis to thyroid (Hematoxylin and eosin x 100)

Figure 7
Bilateral ovarian involvement of Burkitt's Tumor.

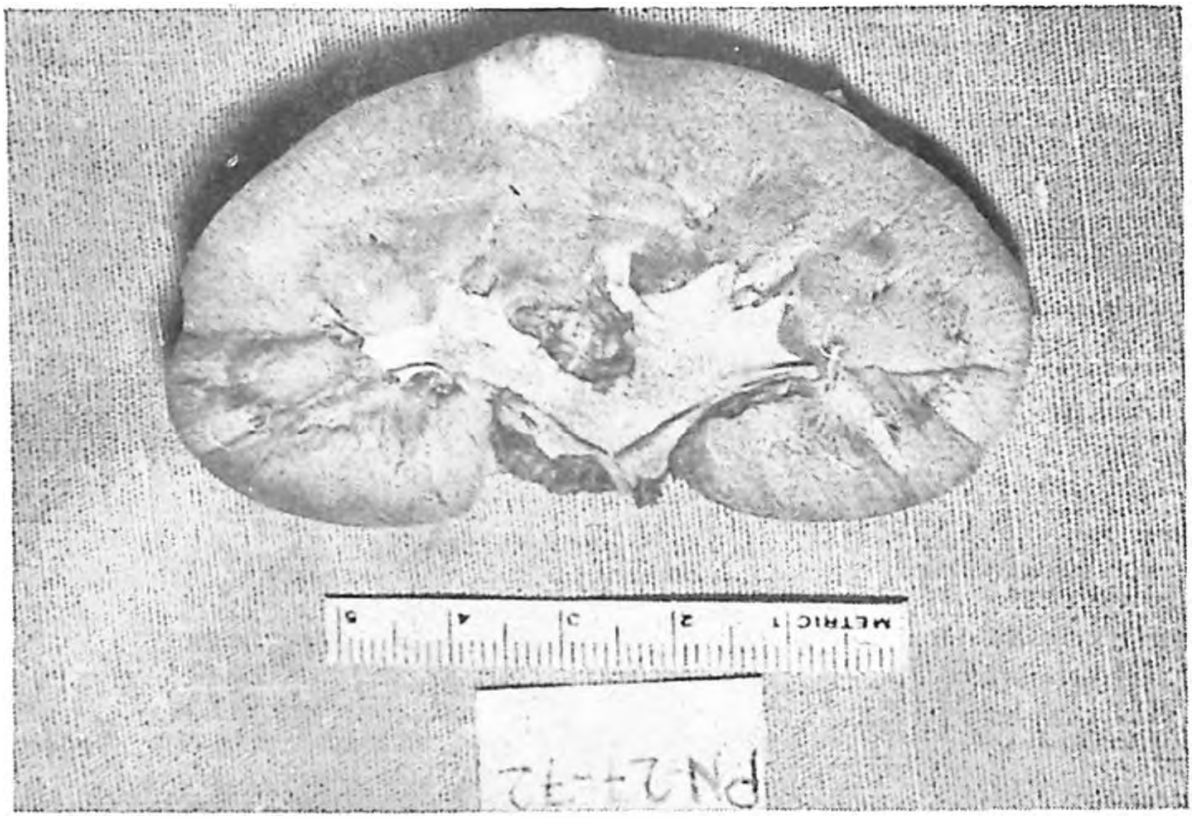


Figure 8
Nodular involvement of kidney

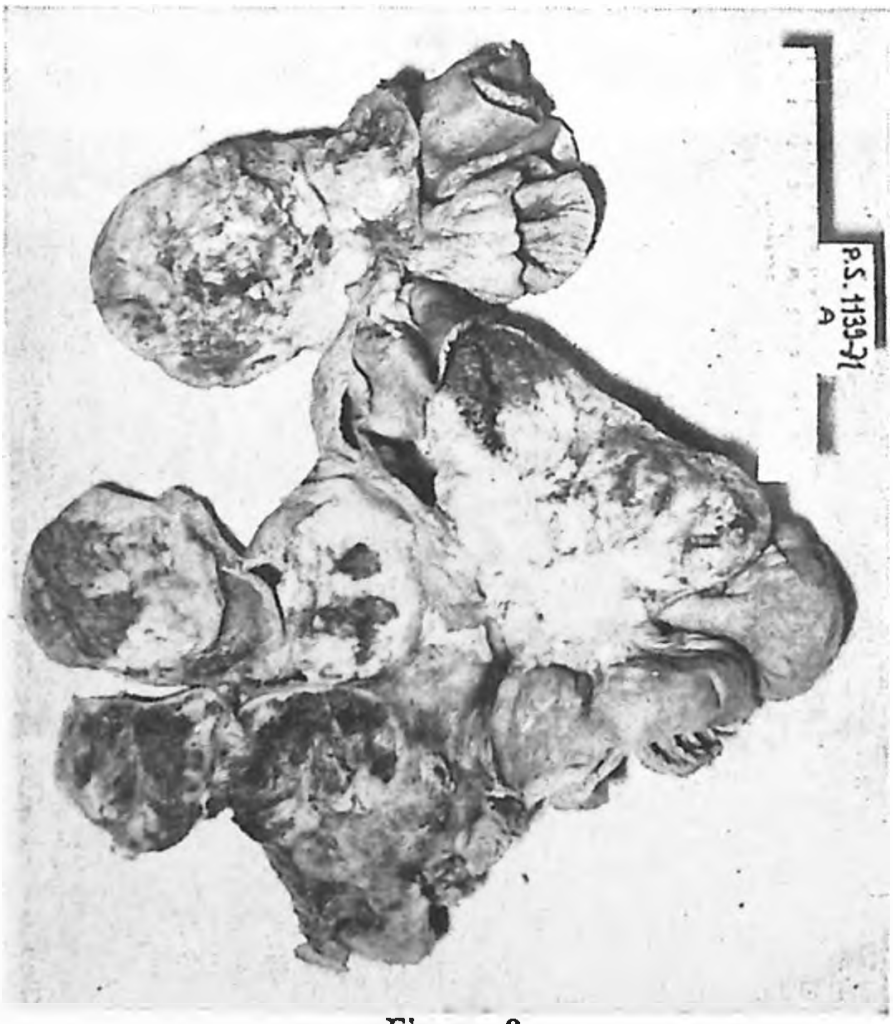


Figure 9
The small and large bowel infiltration of tumor.

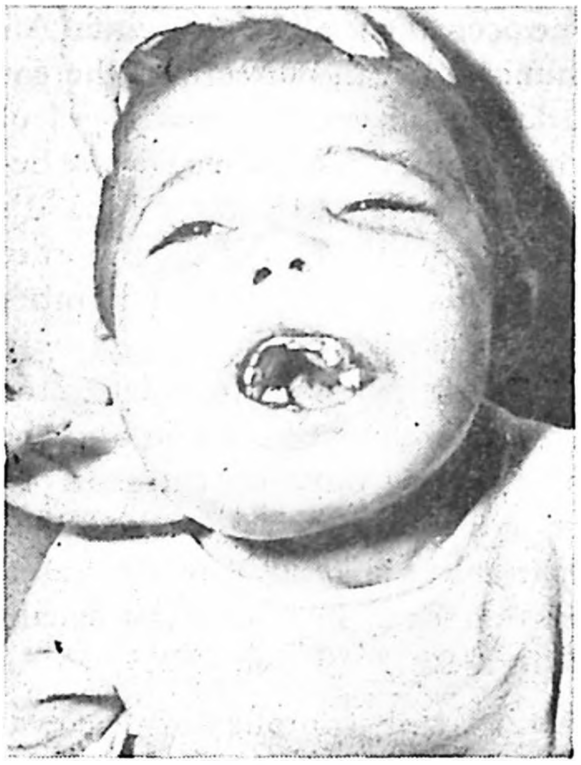


Figure 10
Patient with jaw tumor before treatment with endoxan.

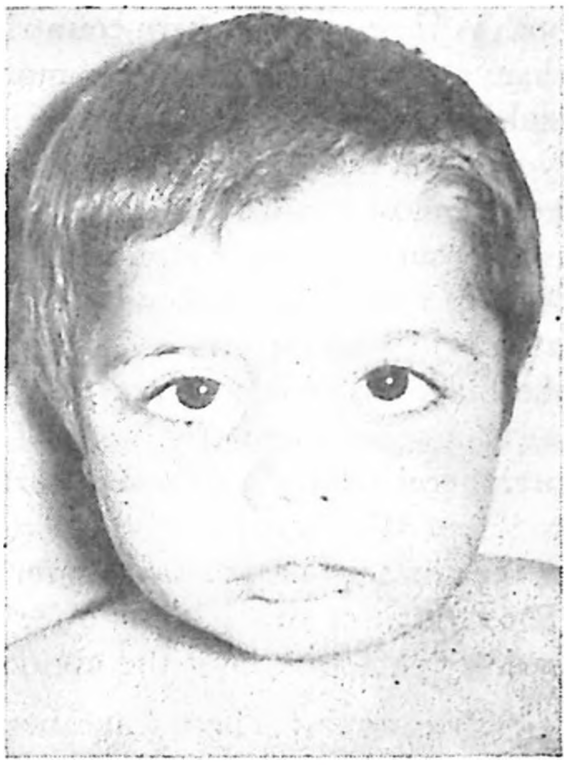


Figure 11
The same patient after treatment with endoxan, showing almost complete regression of tumor.

but 5 months later a recurrence occurred in the other quadrant of the jaw. In 6 out of 20 cases the effect of the treatment could not be evaluated because 3 patients died during the operative period and the other 3 were lost to follow-up. In summary, we were able to follow up 14 out of 20 patients, only 3 were alive and 11, in spite of the two types of treatment, died within an average period of 2.8 months.

Discussion

Burkitt's tumor and malignant tumors seen in Hacettepe Children's Hospital when compared with African children gave both similar and dissimilar findings. Medical centres in Africa have reported that this type of lymphoma is the most frequent tumor and forms 48 to 70 % of all childhood neoplasms[2, 3, 23] In contrast to lymphoma in all African surveys there has been a great deficiency of childhood leukemia and intracranial tumohrs. This is a distinct difference from the Western countries' pattern of "high leukemia, high glioma, low lymphoma".

A review of the Hacettepe Pediatric Pathology Department's records of 893 histologically proven childhood malignancies revealed that leukemia contributes 31%, lymphoma of various types 15.9 %, and brain tumors 15.4 % [24]. This pattern of malignancy is quite unlike those of

both African and Western countries. The occurrence of lymphoma in African children is 3 to 4 times more common than in our series, whereas leukemia is the most common in Turkish children. Various types of lymphoma were the second commonest malignancy, Hodgkin's Disease being the most frequent (96 out of 185 cases of lymphoma) and the Burkitt's type occurred rather infrequently[1]. Since the publication of the report of the first case from Turkey in 1966,[6] we have noted an increased number of Burkitt's tumor every year because of the increased familiarity with the diagnosis. Age and sex distribution in our cases were similar to the African series. Similarly, none of our cases developed leukemia and the peripheral lymph nodes were rarely involved in 1 out of 20 cases. In our series an abdominal tumor was a common presenting feature in 70 % of the cases, whereas a jaw tumor was present in only 20 % of the cases. The reverse of this is untrue for African children in whom jaw localization is 50-60 % and the abdominal form 30 % (Table IV).[2, 4, 22, 25]

Prognosis: There have been several factors complicating the evaluation of the prognosis in our series. These are: different attitudes of the patients of their families, variations in the treatment used, the limited number of cases, and difficulties in follow-up. However, with these difficulties in mind we have obtained a mean of 2.8 months survival time which indicates a very grave prognosis. Since 70 % of our cases were the abdominal form, it may be a factor affecting the prognosis. In addition to location of the tumor and the form of therapy affecting the prognosis, host immunity is a factor also documented in the literature.[2, 25] Although in our cases no immunological studies were done, we have obtained indirect evidence for this matter. Au (Australia) antigen was investigated in 50 malignant tumors of children seen in Hacettepe Children's Hospital and only significant positivity was obtained with Burkitt's tumor (4 out of 5 cases).[26] In 3 of these Au antigen-positive patients, liver biopsy showed clinically symptomless chronic hepatitis.[27] This finding suggests another indication of imparied immunity in these patients.

Summary

Clinical and pathological aspects of 20 cases of Burkitt's tumor diagnosed in the Department of Pediatric Pathology of Hacettepe Childden's Hospital are reviewed. Similar and dissimilar features are compared with Burkitt's tumor in African children.

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