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SKIN INVOLVEMENT IN CHILDREN WITH NON – HODGKIN'S LYMPHOMA*

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SUMMARY: Büyükpamukçu M, İlhan İ, Çağlar M, Akyüz C, Berberoğlu S, Kotiloğlu E. (Oncology and Pathology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Skin involvement in children with non-Hodgkin's lymphoma. Turk J Pediatr 1995; 37: 117-123.

This study was performed to present our clinical experience with patients with cutaneous malignant lymphoma. Eight of 856 (1%) patients admitted to Hacettepe University Pediatric Oncology Department were diagnosed with skin involvement of non-Hodgkin's lymphoma between November 1971 and December 1992. At the time of diagnosis, the mean patient age was 9.5 years (range 4-15). The male-to-female ratio was 1.7:1. Three of the eight cases had primary cutaneous lymphoma, four had non-Hodgkin's lymphoma (NHL) with skin involvement and one case cutaneous lymphoma as a part of advanced stage NHL. According to Murphy's clinical classification, three cases with primary cutaneous lymphoma were in stage I E, two of the remaining five patients were in stage III and three patients with organ involvement were in stage IV. All eight patients' skin lesions were 6 to 10 cm in diameter, hyperemic, firm and nodular. The skin of the head and neck region, especially the right cheek, was the most involved area. In primary cutaneous lymphomas, the duration between involvement and diagnosis was two to six months. All but two patients received the LSA2 L2 protocol. The other two were treated with the COP protocol and a modified COMP protocol. Three patients in stage I E are now living disease-free. One of the two patients in stage III is disease-free, and the other is in the fifth month of therapy with very advanced disease and is lost to follow-up. Among the three patients in stage IV, one was living disease-free for 38 months after diagnosis, while the other two patients are still under therapy without disease. In our opinion, patients with cutaneous NHL who have different clinical properties need special treatment modalities and advanced immunohistologic studies. *Key words: skin involvement, non-Hodgkin's lymphoma, childhood.*

In large series of Non-Hodgkin's lymphoma (NHL), cutaneous involvement occurs in one to five percent of cases, a rate which is similar in adults and children[1,2]. Patients with cutaneous malignant lymphoma are divided into three groups:

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1. Only skin is involved (primary skin lymphoma); 2. Other organs besides skin are also infiltrated; and 3. No skin involvement at first, but at the advanced stages, the disease spreads to skin[3].

Because of low case numbers and variations of case selection criteria, histopathologic classifications, staging systems and treatment methods, comparison of NHL cases with skin involvement is difficult[1,4].

The aim of this report is to present eight cases of NHL with skin involvement and to introduce our experience with treatment and prognosis of this condition.

Material and Methods

Of 856 patients admitted to Hacettepe University's Pediatric Oncology Department, eight patients (1%) were diagnosed histopathologically with cutaneous NHL between November 1971 and December 1992. In all patients, clinical history, physical examination, whole blood counts, blood chemistry, bone marrow aspiration and/or biopsy, chest x-ray and abdominal ultrasonography were performed for clinical evaluation. Patients were classified according to Murphy's classification[5], and histopathologic evaluation was performed on the basis of the Working Formulation[6].

Results

In our study, the age of the patients at the time of diagnosis was 4-15 years, with a mean age of 9.5 years. Three out of eight cases had primary skin lymphoma, four non-Hodgkin's lymphoma with skin involvement, and the other was a patient with NHL in whom skin involvement occurred during dissemination of the disease.

According to Murphy's Clinical Classification, three cases with primary cutaneous lymphoma were in stage I E, two of the other five patients were in stage III and three patients with organ involvement were in stage IV. One of these three patients had bone marrow infiltration. Skin lesions were approximately 6-10 cm in diameter, hyperemic, firm and nodular. In patients with skin and other organ involvement, the diagnosis was made by histopathological study of the skin obtained together with regional lymph nodes. The hyperemic subcutaneous nodule with infiltration and edema which was palpated on the abdomen of the stage IV patient was considered to be dissemination of disease; therefore a biopsy was not obtained.

The sites most commonly involved were the skin of the head and neck. It is of interest that in all three primary cutaneous lymphoma cases and one stage IV case, the site of involvement was the skin of the cheek (Figs. 1-3). Abdominal skin was the second-most involved area.

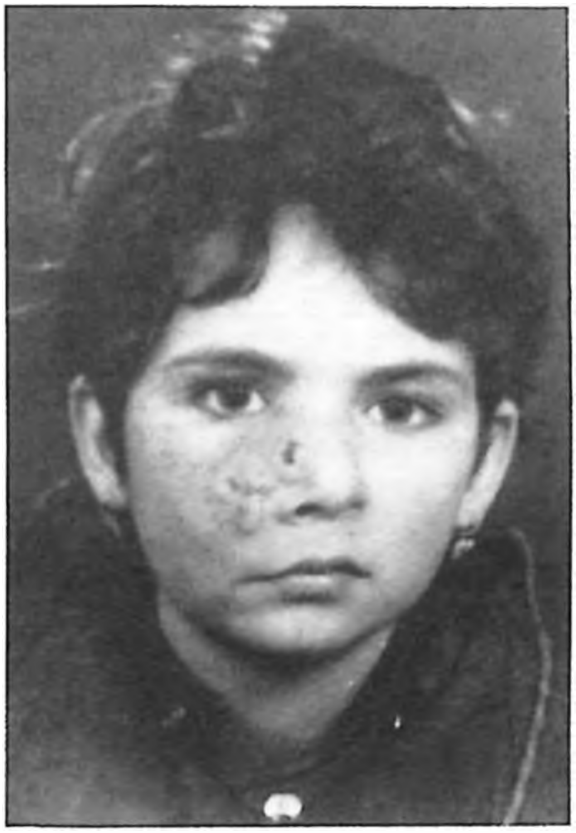
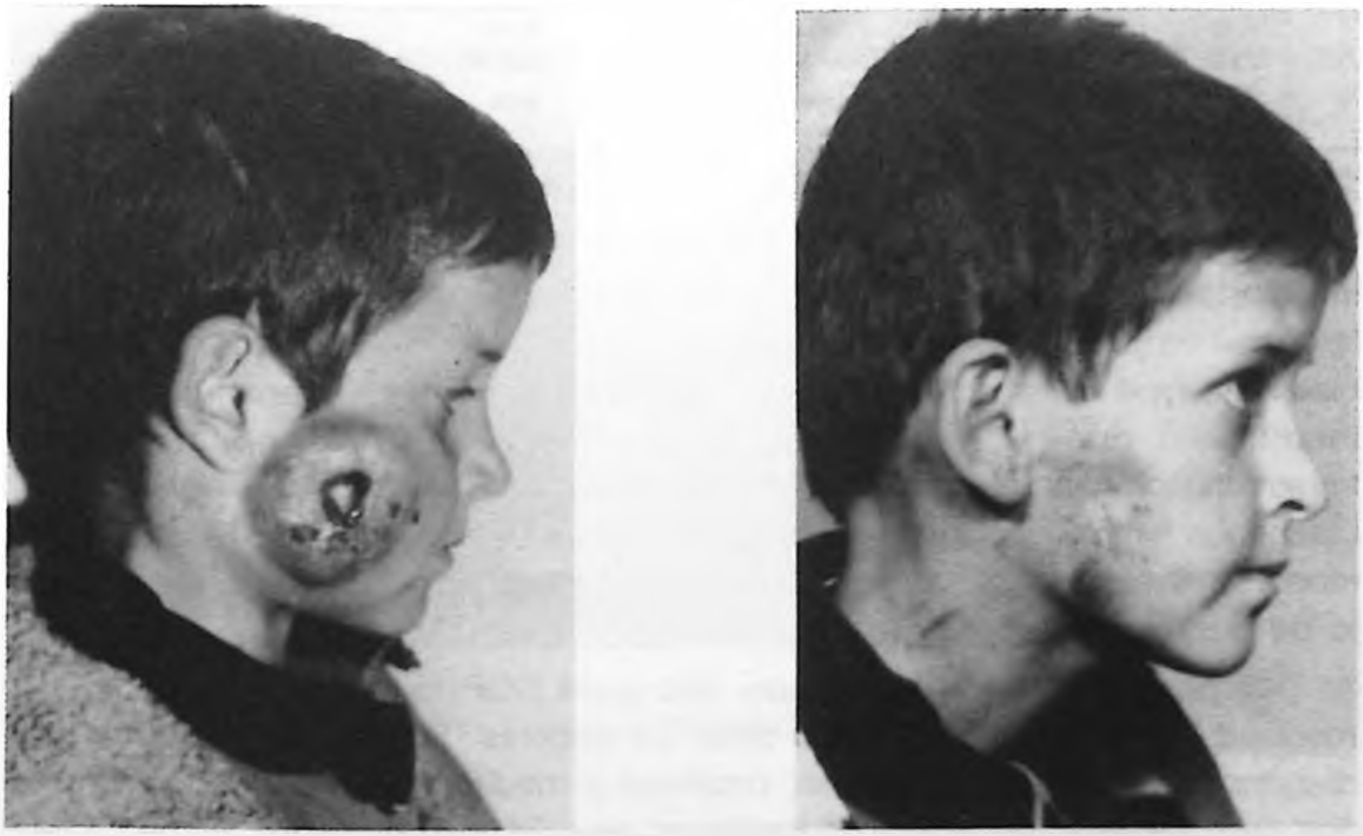


Fig. 1: An irregular lesion on the right cheek (Case 6).



Figs. 2-3: The patient with a large, hard mass on the right cheek at the time of first admission, and appearance after induction therapy (Case 7).

The time interval between the occurrence of the lesion and histopathological diagnosis was one to six months. In patients with primary skin involvement of NHL, systemic involvement did not occur until the last check-up. Clinical and laboratory findings of patients are presented in Table I.

Table I: Selected Characteristics of Patients with Skin Involvement of Non-Hodgkin's Lymphoma

Patient No.	Age* Sex (years)	Duration of Symptoms (months)	Stage	Histopathologic Subgroup	Lesion Region	Other Organ Involvement	Therapy (duration)	Survival and Status
1	11F	2	I E	Lymphoblastic	Right cheek	None	COP 24 months	NED 36 months
2	4 M	1	IV	Large cell/ anaplastic	Right cervical	Cervical Supraclavicular Axillary LAP Liver, spleen	LSA2 L2 26 months	NED 38 months
3	7 F	6	I E	Lymphoblastic	Right cheek	None	LSA2 L2 24 months	NED 36 months
4	4 M	1	III	Small convoluted non-Burkitt	Abdominal wall	Mesenteric mass	LSA2 L2 5 months	Quit in the 5th month
5	15 M	2	III	Large cell immunoblastic	Abdominal wall	Supraclavicular Left axillary LAP	LSA2 L2 17th month replapse than BFM	Death 12 months from relapse
6	10 F	5	I E	Unclassified	Right cheek	None	LSA2 L2	NED 17 months
7	11 M	3	IV	Unclassified	Right cheek	Bone marrow	LSA L2	Under therapy 10th month
8	9 M	1	IV	Unclassified	Abdominal wall	Bone Thyroid	COMP	Under therapy 9th month

Male : male.
LAP : lymphadenopathy.
NED : No evidence of disease.

In histopathologic assessments of cutaneous lymphoma, two lymphoblastic, two large cell immunoblastic/anaplastic and one small cell non-convoluted, non-Burkitt histologic type were identified (Figs. 3-5). In three referral patients, because of insufficient material the subgroup identification could not be made. Immunohistologic assessment was performed in only one case with primary cutaneous lymphoma and one case with stage IV; HLA-DR, CD19 and CD20 monoclonal antibodies, which are primary B lymphocyte markers, were found to be positive in both cases.

All patients received chemotherapy. We gave COP in the first case and the modified LSA2 L2 protocol to the other six patients. The last patient, who was diagnosed with B-cell lymphoma, received a modified COMP protocol. In the first two, the average length of treatment was 24 months, while in the COMP protocol, the treatment length was 12 months. Two of three patients with primary cutaneous lymphoma had been in remission for three years, while the other's

remission duration was 17 months. One of the two patients with cutaneous and extracutaneous NHL has been disease-free for 38 months, while the other patient progressed to systemic disease in the 17th month of therapy died 12 months after the relapse and 27 months following the first diagnosis, although a new therapy protocol had been started (Table I).

Of the patients who were in stage IV at the first diagnosis, one patient developed an early relapse in the second month of therapy and bilateral kidney and skin involvement were observed, but the patient chose not to continue with treatment and follow-up. The other two patients in stage IV were still under therapy and disease free after 9 and 10 months.

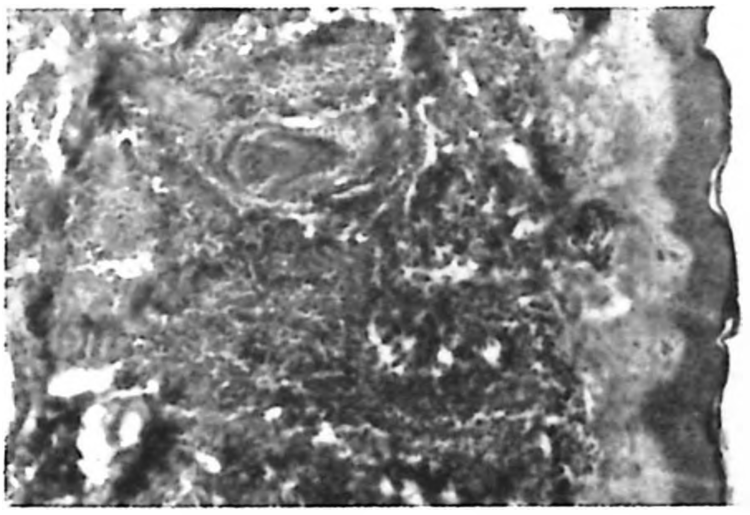


Fig. 4: Diffuse infiltration of lymphoblastic cells in the dermis (H + E, original magnification x 33).

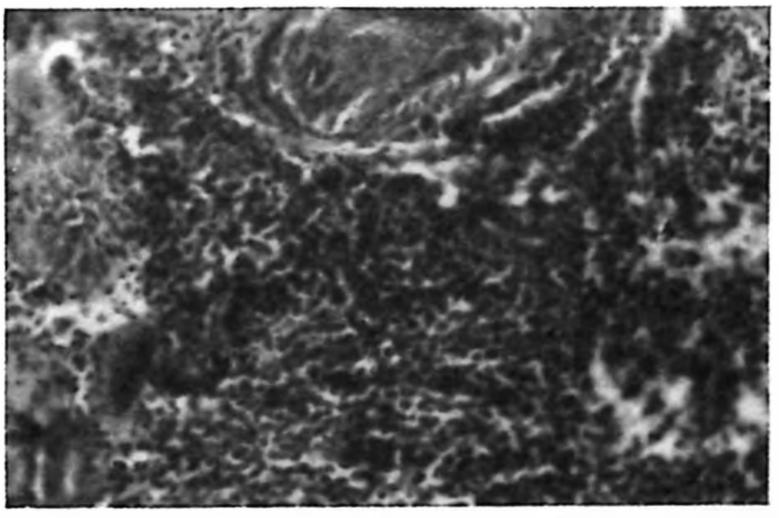


Fig. 5: Lymphoblastic cells surrounding a hair follicle and eccrine glands (H + E, original magnification x 66).

Discussion

It is often difficult to make a correct diagnosis due to the clinical appearance of malignant lymphomas in the skin. This causes some confusion in the differential

diagnosis of some benign lymphoreticular diseases with malignant lymphomas, such as: cutaneous lymphoid hyperplasia, cutaneous lymphoplasia, lymphocytoma cutis, lymphadenosis benigna cutis, reactive lymphoid hyperplasia, Spiegler-Fendt sarcoid, insect bite granuloma, pytriasis lychenoides, varialiformis acuta and pseudolymphomas[7,8].

Primary cutaneous lymphoma is a rare disease, and in some published articles this condition is presented to be a late finding of the disease[9].

The primary disease in the skin may be subclinical for months or even years before histopathological diagnosis. In a report of six cases by Shelly et al.[10], the duration between histopathologic diagnosis and the occurrence of the lesion varied from one to eight years. Skin involvement of lymphoma in reports is generally a solitary, hyperemic nodule, often in the head on neck, similar to our four cases.

Histopathologically and immunohistologically, skin lymphoma is a heterogenous disease. On the other hand, histopathological and immunohistological studies are very rare in this disease. The diagnosis of subgroups of NHL in children varies in different series. Based on the published large series, lymphoblastic lymphoma and large cell lymphoma are the two most commonly encountered types[1-4,11]. In our study, two cases were lymphoblastic, and two cases had large cell NHL similar to those findings. Approximately 50 percent of primary skin NHL is of T-cell origin, and the remaining is of B-cell origin, whereas non-T and non-B lymphomas are very rare[11]. Only two cases in which we could perform immunohistology showed that the origin was B-cell.

There are various treatment modalities. Contrary to the studies that propose only radiation, because of the high relapse rate with this therapy many reports suggest radiation therapy plus chemotherapy or chemotherapy alone[1,2,7]. We administered chemotherapy to all our patients. The prognosis of skin lymphoma depends on the histopathology and stage of disease[1]. When compared to skin and non-skin large cell NHL, primary skin large cell NHL is associated with prolonged survival. While some authors have showed that even if these lymphomas were limited to the skin they could still have a bad prognosis, others have indicated a better overall prognosis[1,2,12-14]. In general, the time interval between occurrence of primary skin lymphoma and systemic illness is six months to five years. In our cases, none of the primary skin lymphomas showed systemic disease.

In conclusion, although the disease is not very commonly seen, we believe that it has a better prognosis than that with other organ involvement. Studies must be done regarding the selection of clinical, histopathologic and immunohistologic assessments as well as treatment protocols for skin lymphomas.

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