

The Spectrum of Cutaneous Lymphomas in Patients Less than 20 Years of Age

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Abstract: Cutaneous lymphomas are rare in young patients and are mostly represented by mycosis fungoides and its variants and CD30⁺ lymphoproliferative disorders (lymphomatoid papulosis [LYP] and anaplastic large T-cell lymphoma). We report our observations in a series of 69 patients less than 20 years of age who presented either with primary cutaneous lymphoma ($n = 62$) or with secondary manifestations of extracutaneous disease ($n = 7$). Clinicopathologic features permitted classification of the cases into the following diagnostic categories: mycosis fungoides ($n = 24$, all primary cutaneous), anaplastic large T-cell lymphoma ($n = 13$, all primary cutaneous), LYP ($n = 11$, all primary cutaneous), subcutaneous “panniculitis-like” T-cell lymphoma ($n = 1$, primary cutaneous), small-medium pleomorphic T-cell lymphoma ($n = 2$, all primary cutaneous), natural killer (NK)/T-cell lymphoma, nasal-type ($n = 1$, secondary cutaneous), follicle center cell lymphoma ($n = 1$, primary cutaneous), marginal zone B-cell lymphoma ($n = 7$, all primary cutaneous), B-lymphoblastic lymphomas ($n = 6$, 3 primary and 3 secondary cutaneous), specific cutaneous manifestations of Hodgkin disease ($n = 1$, secondary cutaneous), and acute myeloid leukemia ($n = 2$, both secondary cutaneous). Cutaneous lymphoma in children should be differentiated from benign skin disorders that may simulate them. In particular, mycosis fungoides and LYP in this age group may present with clinicopathologic features reminiscent of inflammatory disorders such as pityriasis alba, vitiligo, pityriasis rosea, and pityriasis lichenoides et varioliformis acuta. Even in secondary cutaneous lymphomas, skin manifestations may be the first sign of the systemic disease, and a diagnosis may be achieved on examination of histopathologic specimens of a cutaneous lesion. Our study illustrates the wide spectrum of cutaneous lymphomas and leukemias in patients less than 20 years of age and underlines the need for proper interpretation of these lesions by dermatologists and dermatopathologists.

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B-cell and T-cell non-Hodgkin lymphomas are rare in childhood, accounting for about 6% of malignant neoplasms in children (1). Most of them affect primarily the lymphatic tissue (lymph nodes, thymus) or bone marrow, but sometimes soft tissue, bone (not bone marrow), lung, central nervous system, kidney, and skin can become involved. Skin involvement in non-Hodgkin lymphoma in children represents primary cutaneous lymphoma or a secondary manifestation of extracutaneous disease. In this latter instance, sometimes skin lesions are the first sign of an extracutaneous lymphoma.

Large studies of cutaneous lymphomas in childhood are rare, and only a few cases have been reported. Similar to the situation observed in adult patients, most reported children have mycosis fungoides (2–16), the most common type of cutaneous T-cell lymphoma (CTCL). Other cutaneous lymphomas in children include lymphomatoid papulosis (LYP) (17–23) and primary cutaneous CD30⁺ anaplastic large cell lymphoma (ALCL) (24–31). At present there are few data on primary cutaneous B-cell lymphomas (CBCLs) in childhood (32). The purpose of our study was to report our experience with a group of young patients (less than 20 years of age) with cutaneous lymphoma.

PATIENTS AND METHODS

Patients

Data from 69 patients collected from the files of the Department of Dermatology, University of Graz, Graz, Austria and the Department of Pathology, University of Vienna, Vienna, Austria between 1960 and 2002 were included in this study. Some cases represented consultations from other centers. Primary skin involvement was defined as the presence of cutaneous lymphoma without nodal and/or visceral involvement after complete staging procedures (33). Staging procedures were performed with standard methods available at the time of first diagnosis, including physical examination, blood cell count, chest radiograph, thoracic computed tomography (CT) scan, abdominal ultrasound sonography, abdominal CT scan, sonography of superficial lymph nodes, and bone marrow biopsy. In each case, the original diagnosis was reviewed by at least two dermatopathologists (L.C., H.K.) based on clinicopathologic criteria. Cases were classified according to the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group classification of cutaneous lymphomas (34) and the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues (35).

Clinical data analyzed included patient age, sex, date of first diagnosis, duration of follow-up, and status of the

disease at last follow-up. Therapy effects were not included in our study. The following parameters were selected to assess the status of the patient at the endpoint of follow-up: A⁻, alive and well; A⁺, alive with skin disease; A⁺⁺, alive with extracutaneous disease; D⁺, patient dead of lymphoma; D⁻, patient dead of unrelated causes.

Histology, Immunohistology, and Molecular Biology

Sections with a maximum thickness of 4 μm stained with hematoxylin-eosin, Giemsa, and periodic acid-Schiff (PAS) stains were available for standard histologic evaluation. Immunophenotyping was performed on formalin-fixed, paraffin-embedded tissue sections using a three-step immunoperoxidase technique as described previously (36), with a broad panel of monoclonal antibodies. Microwave enhancement was used for several antibodies. Second and third antibodies were obtained from DAKO (Glostrup, Denmark).

In all cases in which a paraffin block could be retrieved, analysis of the T-cell receptor (TCR) and immunoglobulin heavy chain (IgH/J_H) gene rearrangement was performed using polymerase chain reaction (PCR) techniques and primers as published previously (37,38) with minor modifications (39). Details on PCR procedures have been published previously (40).

Statistical analyses were performed using the SPSS/PC statistical software package (SPSS Inc., Chicago, IL).

RESULTS

A total of 69 children (33 male, 36 female) were included in the study. Ages ranged from 1 to 20 years (mean 14; median 16). Exact classifications and clinical data for each entity are reported in Tables 1 and 2.

Follow-up data were available for 45 patients (65.2%). Patients were followed up from a minimum of 1 month to a maximum of 335 months (mean 68.9 months; median 24 months).

ADDITIONAL OBSERVATIONS

Mycosis Fungoides

Peculiar presentations included hypopigmented mycosis fungoides (three cases) (Fig. 1), localized pagetoid reticulosis (three cases), and mycosis fungoides associated with follicular mucinosis (one case). Cases of so-called idiopathic follicular mucinosis (41) and of small-plaque parapsoriasis were not included in the study. Stages according to the TNM staging system were as follows: IA, 13 patients; IB, 10 patients; IIB, 1 patient.

TABLE 1. Classification and Clinical Data for Cutaneous Lymphomas in 69 Patients Less than 20 Years of Age

Diagnosis	Number of patients	Primary cutaneous (yes/no)	Sex (male:female)	Mean/median age (years) ^a	Mean/median follow-up (months) ^a	Status
Mycosis fungoides	24	24/0	12:12	15.2/17 (3–20)	83/18 (4–335); <i>n</i> = 17	A ⁻ : 6; A ⁺ : 11
CD30 ⁺ ALCL	13	13/0	7:6	13.5/14 (3–19)	26.8/9.5 (4–84); <i>n</i> = 4	A ⁻ : 2; A ⁺⁺ : 1 ^b ; D ⁻ : 1
LYP	11	11/0	5:6	12.9/12 (4–19)	55.7/31.5 (1–240); <i>n</i> = 10	A ⁺ : 10 ^c
Subcutaneous “panniculitis-like” T-cell lymphoma	1	1/0	0:1	20-year-old	NA	
Small/medium-size pleomorphic CTCL	2	2/0	1:1	18/18 (16–20)	22/22 (16–28); <i>n</i> = 2	A ⁻ : 2
NK/T cell lymphoma, nasal type	1	0/1 ^d	0:1	15-year-old	4	D ⁺ : 1
FCCL	1	1/0	0:1	20-year-old	13	A ⁺ : 1
MZL	7	7/0	2:5	17/17 (12–20)	46.7/28 (3–128); <i>n</i> = 4	A ⁻ : 2; A ⁺ : 2
B-lymphoblastic lymphoma	6	3/3 ^e	5:1	6.6/5.5 (1–18)	153.4/157 (7–287); <i>n</i> = 5	A ⁻ : 5
Hodgkin disease	1	0/1	1:0	20-year-old	NA	
Acute myelogenous leukemia	2	0/2	0:2	10.5/10.5 (2–19)	13; <i>n</i> = 1	D ⁺ : 1

^aRange in parentheses.

^bThe patient developed involvement of regional lymph nodes.

^cFour patients with recurrent lesions during follow-up presented without skin manifestations of LYP at the last follow-up visit.

^dThe patient presented with skin lesions as the first sign of lymphoma of the nasal cavity.

^eTwo of the three patients with secondary cutaneous B-lymphoblastic lymphoma presented with skin lesions as the first manifestation of the disease. A⁻, alive and well; A⁺, alive with skin disease; A⁺⁺, alive with extracutaneous disease; D⁺, dead of lymphoma; D⁻, dead of unrelated causes NA, not available.

CD30⁺ ALCL (Fig. 2)

Peculiar presentations included small-cell-type ALCL (one case) and inflammatory-type ALCL simulating LYP (one case).

Lymphomatoid Papulosis (Fig. 3)

Nine patients were histologic type A; the other two patients presented with lesions showing different histologic types (A/B, one patient; A/C, one patient). Peculiar presentations included regional LYP (lesions clustered on a single region of the skin) in three patients and follicular LYP (lesions centered around hair follicles) in two patients.

Marginal Zone Lymphoma

One patient (Fig. 4) achieved complete remission after antibiotic treatment (ceftriaxone 1 g/day for 3 weeks). In this patient, PCR analysis for *Borrelia burgdorferi* DNA performed according to procedures described previously (42) revealed a positive reaction.

B-Lymphoblastic Lymphoma (Fig. 5)

Three patients had negative staging at presentation. Two patients with extracutaneous B-lymphoblastic lymphoma presented with skin lesions as the first manifestation of the disease.

DISCUSSION

This is the largest series of young patients with cutaneous lymphomas. Although most patients in our study (89.9%) had primary cutaneous lymphoma, it is likely that in many instances secondary skin lesions in young patients with known systemic lymphoma are not biopsied or removed, as the diagnosis has already been established and regression of specific cutaneous manifestations under treatment is an important sign of the efficacy of the therapy. Thus we cannot draw conclusions about the true relative frequency of specific cutaneous lesions in systemic lymphoma of children. It is important to note, however, that three of the seven cases of secondary cutaneous lymphoma represented patients presenting primarily to dermatologists (the skin first manifested the disease) (see Table 1), indicating that the diagnosis of a systemic lymphoma in some patients is achieved by biopsy of skin lesions.

Of the patients included in our study, 34.8% had mycosis fungoides, confirming that this is the most common form of cutaneous lymphoma in childhood and adolescence. In general, mycosis fungoides in patients younger than 20 years of age is rare, but the true incidence may be higher than generally assumed because there is often a reluctance to perform biopsies in children, and the diagnosis can be delayed for several years (43,44). In fact, we have seen several adult patients with mycosis fungoides who noted the onset of their skin disease in adolescence (data not shown).

In our study, two children had the hypopigmented variant of mycosis fungoides. Hypopigmented mycosis



Figure 1. Mycosis fungoides in a 14-year-old boy. Note the scaly erythematous plaque on the trunk, with smaller patches in the vicinity.



Figure 2. CD30⁺ ALCL in a 14-year-old boy. Note the large solitary tumor on the chest.



Figure 3. LYP in a 7-year-old child. Note the small erythematous nodule and small papules on the lower arm.

fungoides has been described in children (7,13,45–55), especially in those with dark skin, and for unknown reasons has an unusually high frequency in this age group (56). Hypopigmented mycosis fungoides may be mistaken for a variety of benign entities including vitiligo, lichen sclerosus et atrophicus, or pityriasis alba. The high frequency of hypopigmented mycosis fungoides in children emphasizes the need to consider mycosis fungoides in the differential diagnosis of chronic hypopigmented dermatoses for early diagnosis of the disease (56,57).

Only one of our patients had mycosis fungoides-associated follicular mucinosis. Although we recently suggested that idiopathic follicular mucinosis may represent a variant of mycosis fungoides (41), we did not include patients with idiopathic follicular mucinosis in this study, as precise classification of this disease and its association with mycosis fungoides are still controversial (41,58). However, follicular mucinosis associated with mycosis fungoides has been reported in children (4,11,59–61), and

the findings in our patient's confirm once more that age alone is not sufficient to exclude a diagnosis of mycosis fungoides in these patients. In our database we found six patients with idiopathic follicular mucinosis less than 20 years of age, 4 of whom were included in a previous study on follicular mucinosis (41).

Granulomatous slack skin has been described in a young patient (62), but none of the patients in our study had a granulomatous variant of mycosis fungoides. It is interesting that 3 of 24 patients with mycosis fungoides (12.5%) had localized pagetoid reticulosis (Woringer-Kolopp type). The relatively high percentage of this finding raises the question as to whether this variant of mycosis fungoides occurs more frequently in childhood. The clinical presentation can be deceiving, and often lesions will be biopsied only after prolonged local treatments (63). Indeed, in one of our patients the keratotic lesions on one



Figure 4. Marginal zone B-cell lymphoma in a 12-year-old girl. Note the erythematous nodule on the arm. The patient had two similar lesions on the other arm.



Figure 5. B-lymphoblastic lymphoma in a 2-year-old girl. Note the large reddish tumor on the face.

foot were previously diagnosed and treated as warts before a biopsy established the correct diagnosis.

The overall outlook for children and adolescents with mycosis fungoides is difficult to predict, and it has been maintained that mycosis fungoides is more aggressive in childhood, with a higher frequency of extracutaneous involvement (7,11,64). Other authors, however, have suggested that the natural history of the disease is comparable to that seen in adults (12,16). Indeed, it may be that at least some of the cases reported in the past as “atypical” mycosis fungoides in children represent, in fact, examples of the so-called cytotoxic lymphomas, which usually have a more aggressive course and poorer prognosis. In our study, none of the 17 patients with mycosis fungoides and available follow-up data developed systemic disease or died because of disseminated lymphoma. However, median follow-up was only 18 months, and 11 patients had skin lesions of mycosis fungoides at the endpoint follow-up. In this context, it seems likely that the onset of lesions of mycosis fungoides as early as childhood may

increase the probability of disease progression during the patients lifetime.

We had no patients with Sézary syndrome, a leukemic form of CTCL, and only two cases have been reported in the literature (43,65). A few instances of cutaneous lesions in human T-lymphotropic virus I (HTLV-I)-associated adult-T-cell leukemia/lymphoma (ATLL) have been reported in children (66–68), one of them with granulomatous features (69). However, HTLV-I-associated diseases are extremely rare outside endemic areas (Japan, Caribbean basin, South and Central America, and the south-eastern United States), and are virtually unknown in Europe.

In our study we observed one patient with concurrent cutaneous and nasal mucosa manifestations of natural killer (NK)/T-cell lymphoma, nasal-type, one with subcutaneous lymphoma, and two with so-called small-medium-sized pleomorphic CTCL. Reports of these lymphomas in children are very rare, especially in Western countries (70,71). In some regions of the world a peculiar type of CTCL with hydroa vacciniformis-like clinical manifestations has

TABLE 2. Cutaneous Lymphomas Observed in Our Study and Corresponding Categories According to the EORTC and WHO Classifications

Present study	EORTC classification	WHO classification
Mycosis fungoides	Mycosis fungoides Mycosis fungoides-associated follicular mucinosis Pagetoid reticulosis	Mycosis fungoides/Sezary syndrome
LYP	LYP	ALCL, primary cutaneous type (including LYP)
Large cell CTCL, CD 30 ⁺	Large cell CTCL, CD 30 ⁺	
CTCL, pleomorphic, small/ medium-size	CTCL, pleomorphic, small/medium-size (provisional entity)	Peripheral T-cell lymphoma, not otherwise characterized
Primary cutaneous NK/T-cell lymphoma, nasal type	Large cell CTCL, CD30 ⁻	Extranodal NK/T-cell lymphoma, nasal type
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma (provisional entity)	Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous marginal zone B-cell lymphoma	Primary cutaneous immunocytoma/marginal zone B-cell lymphoma	Extranodal MZL of MALT type
Primary cutaneous FCCL	Primary cutaneous FCCL	Follicular lymphoma Diffuse large B-cell lymphoma
B lymphoblastic lymphoma	No corresponding category	Precursor B lymphoblastic leukemia/lymphoblastic lymphoma
Hodgkin disease	No corresponding category	Hodgkin lymphoma (various subtypes)
Acute myelogenous leukemia	No corresponding category	Acute myeloid leukemia (various subtypes)

been described (72–74), but we had no patient with this aggressive variant of cytotoxic T-cell lymphoma in our study. A few instances of cutaneous aggressive T-cell lymphoma have also been observed in Western countries in immunocompromised children (congenital [human immunodeficiency virus] HIV infection, immunosuppression consequent to organ transplantation, aggressive chemotherapeutic regimens), underlining the need for careful long-term follow-up in these patients (75).

Thirteen patients in our study had CD30⁺ ALCL. Although primary nodal CD30⁺ ALCL is common in childhood and adolescence, primary cutaneous cases are relatively uncommon before the age of 20 years (25,26,28,30,31). Unusual presentations of ALCL in our group included one patient with a small to medium-size morphology of neoplastic cells (the so-called small-cell variant of ALCL) (76), and one with histopathologic features simulating LYP. Patients similar to this last one have been reported in the past as “borderline ALCL-LYP,” and can be classified correctly only upon precise clinicopathologic correlation (77,78). Primary cutaneous ALCL is considered to be a form of CTCL with excellent prognosis, and may be treated with simple excision and/or local radiotherapy (33,35,79). Experience in children and adolescents, however, is still limited, and long-term follow-up must be recommended. In our series, one patient with negative staging at presentation developed systemic disease after a follow-up of 6 months, but we cannot exclude completely that he had a secondary manifestation of primary nodal disease. In fact, staining of the skin lesion for ALK-1 revealed focally a weak positivity. Unfortunately we could not retrieve the ALK status of the nodal tumor.

Eleven children in our study had LYP. Although in past years LYP has been considered as a paradigmatic example of the cutaneous “pseudolymphomas,” it is now widely considered as a low-grade malignant CTCL and it is included as such in the two major classification schemes of lymphomas (WHO, EORTC) (34,35). Clinical diagnosis of LYP can be difficult because the disease is rare and often there is a reluctance to perform biopsies of lesions that resolve without treatment. The differential diagnosis with pityriasis lichenoides et varioliformis acuta (PLEVA) can be extremely difficult, and there is much confusion in the literature concerning the relationship between these two entities and the existence of PLEVA-associated CTCL (8,80,81).

Another problem is the fact that, if biopsied, histologic features of LYP might be interpreted as high-grade lymphoma, thus leading to unnecessarily aggressive treatment. In particular, so-called regional LYP must be differentiated from CD30⁺ ALCL. Regional LYP was diagnosed in 3 of our 11 patients with LYP (27.3%). This variant of the disease has been described very rarely in adults (82), and it may be that it occurs more often in children. However, differentiation from cutaneous ALCL, which can also show clustered lesions with partial resolution, is very difficult, and in our opinion staging investigations should be performed and patients should be followed-up very carefully. Although in a small percentage of patients association of LYP with other lymphomas has been described (21,22), the prognosis is excellent (estimated 5-year survival rate of 100%) (33,35), thus treatment is not necessarily recommended. On the other hand, long-term follow-up is mandatory.

Primary CBCLs have seldom been described in children, therefore no exact data concerning prognosis and management exist (32). In our study we had seven patients with marginal zone lymphoma (MZL) and one with follicle center cell lymphoma (FCCL). Differential diagnosis of indolent CBCLs includes mainly reactive infiltrates of B lymphocytes (lymphadenosis benigna cutis), and distinction may be difficult in some cases (57). In fact, at least some of the lesions classified in the past as B-cell pseudolymphoma have been reclassified later as indolent CBCL, especially MZL (39). The prognosis of cutaneous MZL and FCCL in adult patients is very good; the estimated 5-year survival is greater than 90% for both (33,35). As already described for adults (83–85), in one of our young patients with MZL (in whom *B. burgdorferi* DNA could be demonstrated within skin lesions by PCR), complete remission was achieved with antibiotic treatment. Especially in areas endemic for *B. burgdorferi* infection, antibiotic treatment should always be considered when planning MZL therapy (39).

Six of our patients had an aggressive type of B-cell lymphoma, namely, B-lymphoblastic lymphoma (B-LBL). Although in most patients skin lesions of B-LBL are secondary to nodal or leukemic disease, in a few cases B-LBL is apparently limited to the skin (86–88). A similar situation could be observed in three of our six patients, who had cutaneous B-LBL with negative staging investigations. It is important to emphasize that at present, management of B-LBL does not differ in patients with or without extracutaneous involvement, and that all those affected should be treated with standard regimens for B-LBL regardless of the results of staging investigations.

One patient in our group had specific skin manifestations of Hodgkin disease (HD), and two had specific skin manifestations of acute myelogenous leukemia (AML). Nodal HD has been observed rarely in young patients with cutaneous follicular mucinosis (58), but specific skin manifestations of HD have not been reported in this age group. Usually patients develop nonspecific signs of altered immunity due to the tumor or the aggressive treatment, such as opportunistic infections and unusual presentations of common infections (e.g., vegetating herpes simplex). The exact frequency of specific skin manifestations of AML is not known, and usually cutaneous lesions are not biopsied, as the diagnosis has already been established. In rare instances, however, skin manifestations may be the first sign of AML, and a full leukemic picture may even be missing for several months (so-called “aleukemic leukemia cutis”), thus underlining the need for proper identification of these patients based on the typical clinicopathologic findings of skin lesions. Other cutaneous lymphomas in children reported in the literature include a case of specific skin lesions of lymphomatoid granulo-

matosis in a 4-year-old boy (89), but we had no similar patient in our group.

Our study and review of the literature demonstrate that a wide spectrum of primary and secondary cutaneous lymphomas and leukemias can be observed in young patients. Recognition of this spectrum by dermatologists is crucial because, even in secondary cutaneous cases, diagnosis is often established by biopsy of skin lesions.

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