# Primary cutaneous lymphoma in children: A report of four cases

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Primary cutaneous lymphoma (CL) is a malignant lymphoma presenting in the skin. Primary CL is rare in children and difficult to clinically diagnose. We report four pediatric cases of primary CL with tumors in different body area: case 1, on the face and left thigh; case 2, on the left side of the neck; case 3, on the left side of the back; and case 4, on the left buttock. The first diagnoses of these children were rash, abscess, lymphadenitis, and fever, respectively in local hospitals. All 4 patients were diagnosed as primary CL by histopathologic examination in our hospital. Three patients (case 1, case 2 and case 4) were treated with chemotherapy. The size of tumor and degree of cutaneous lesion were alleviated after chemotherapy. Case 3 refused to receive chemotherapy, and died. The cases indicated the importance of early diagnosis of primary CL to guide appropriate therapy.

Key words: primary cutaneous lymphoma, pediatric, biopsy, chemotherapy.

Primary cutaneous lymphoma (CL) is a malignant lymphoma presenting in the skin without extracutaneous dissemination at the time of initial diagnosis, including cutaneous T-cell, B-cell lymphomas and immature hematopoietic malignancies.<sup>1</sup> Primary CL is the second most common type of extranodal non-Hodgkin lymphoma, which accounts for 19% of non-Hodgkin's lymphomas.<sup>2</sup> Primary CL comprises numerous subtypes with various clinical presentations, histopathologic, cytogenetics, molecular features in the skin and subcutaneous tissues.<sup>3</sup> Early diagnosis, accurate classification and staging are important for guiding appropriate treatment for primary CL and would improve prognosis of patients significantly.

Primary CL is rare in children and difficult to diagnose. In this report, we presented four cases of primary CL in childhood with prominent skin lesions. The characteristic histologic and immunophenotypical features, treatment and outcomes of those cases are described.

#### **Case Reports**

Clinical data of the four primary CL cases are summarized in Table I. Informed consents for publication were obtained from the cases.

### Case 1

A 12-year-old girl was referred for examination of asymptomatic swellings on the face and the left thigh area (Fig. 1A). The initial diagnosis was rash, which was made in a local hospital 1 year before. The swellings had reportedly grown over the course of 1 year. The swelling on the left thigh area developed as an inguinal mass (Fig. 1B, 1C). Histopathologic evaluation of a skin biopsy sample from left thigh was performed in a local hospital. The specimen showed that lymphocytic infiltration and atypical lymphoid cells in the dermis and subcutaneous fat layer. Tumor cells had an abnormal size, with less chromatin and disruption of normal nuclear architecture. Some areas had a "starlike" appearance. Computerized tomography (CT) scan showed multiple lesions in the lung. Immunohistochemical staining revealed

		Table I. Clinic	cal Data of the C	ases with Pr	imary Cutaneous Lymphoma.		
Case	Age	Locations of swelling or mass (duration of symptoms)	Initial diagnosis	Subtypes	Atypical lymphoid cells	Chemotherapy	Duration of follow-up
1	12 years	Face, left thigh (1 year) Groin (2 mo.)	Dermatitis (rash)	T-cell	CD3, CD56, LCA, Bcl-6, Ki- 67 (50%),	5 cycles	1 year
2	5 years	Left side of the neck (2 mo.) Cervical lymph nodes (2 weeks)	Abscess, lymphadenitis	B-cell	CD3, CD4, CD8, CD16, CD19, CD45, CD56	28 cycles	3 years
ŝ	11 years	Left side of the back (4 mo.) Left axilla (3 mo.)	Lymphadenitis	T-cell	CD4, CD8, CD16, CD45, CD56	None	3.5 years
4	9 years	Left buttock (1 mo.)	Fever and infectious disease	T-cell	Vimentin, CD3, CD20, S100, CD30, CD8 and Ki-67 (80%).	3 cycles	1 year
Bcl: B-ce	ll leukemia-ly	mphoma, CD: cluster difference, Ki-67:	nuclear- associated	antigen, LCA	t: leucocyte common antigen,		

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**Fig. 1.** Clinical presentation of case 1. A) Appearance of pre-chemotherapy; B) Appearance after the first chemotherapy; C) The whole appearance of the mass; D) The section of the mass.

atypical lymphocytes which were positive for CD3, CD56, leukocyte common antigen (LCA), B-cell lymphoma 6 (Bcl-6), and Ki-67 positivity (50%), but negative for CD4, CD8, CD7a, CD30, ALK, CD15, EBV, TDT, CD34, EMA. She was diagnosed as primary T-cell CL. Now, she has received 5 cycles of chemotherapy: (1) Vincristine (2.8 mg, d1, d8, d15, d22) + prednisone (60 mg d0-d21) + daunorubicin (42 mg, d1, d8, d15) + L-asparaginase (8,500 U: 10 times, d2, d4, d6, d8, d10, d12, d14 , d16, d18, d20); (2) cyclophosphamide (1300 mg, d1) + cytarabine (2,300 mg, q12h; 4 times, d1-d2) + 6-mercaptopurine (100 mg, d1-d7); (3) cyclophosphamide (1375 mg, d1) + cytarabine (70 mg, q12h; 14 times, d1-d7) + 6-mercaptopurine (100 mg, d1-d7); (4) high-dose methotrexate (6 g, d1) + 6-mercaptopurine (33 mg, d1-d14); (5) high—dose methotrexate (6 g, d1) + 6-mercaptopurine (33 mg, d1-d14). After 5 cycles of chemotherapy, the swellings on the face were significantly alleviated (Fig. 1D).

## Case 2

A 5-year-old boy was referred for examination of an erythematous swelling on the left side of his neck. The initial diagnosis in a local hospital was abscess (2 months before). The swelling

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Fig. 2. Clinical presentation of case 2. A) CT scan of the head, the mass can be seen in the left temporal area; B) Tumor histology (hematoxylin and eosin staining,  $100 \times magnification$ ).



Fig. 3. Clinical presentation of case 3. A) CT scan of the chest, the mass can be seen on the left back; B) Tumor histology (hematoxylin and eosin staining,  $100 \times magnification$ ).



Fig. 4. Clinical presentation of case 4. A) Swelling on the left buttock; B) Tumor histology (hematoxylin and eosin staining,  $100 \times magnification$ ).

increased gradually, and lymphadenopathy appeared on the left side 2 weeks prior to our hospital. CT scan showed tumor metastasis in the skull skin (Fig. 2A). Histopathologic evaluation of the skin biopsy showed a panniculitis-like infiltration of atypical lymphoid cells (Fig. 2B). Immunohistochemical staining revealed atypical lymphocytes which were positive for CD3, CD4, CD8, CD16, CD19, CD45, and CD56. Another specimen from the lymph node showed similar findings. He was diagnosed as B-cell cutaneous lymphoma, and was treated with 28 cycles of chemotherapy. The chemotherapy agents were: (1) vindesine (1.6 mg, d1) + dexamethasone(3.1 mg, d1-d7) + pegaspargase (1,600 IU, d1) and (2) cyclophosphamide (730 mg, d1) + cytarabine (70 mg, q12h, 12 times, d1-d6) + 6-mercaptopurine (50 mg, d1-d7) and (3) high-dose methotrexate (3 g, d1) +6-mercaptopurine (50 mg, d1-d7) and (4)

vindesine (1 mg, d1) + daunorubicin (23 mg, d1, d8) + dexamethasone (6 mg, d1-d4) + pegaspargase (1,600IU, d1); the four regimens were implemented in turn. Two years later, the lymphoma recurred, the chemotherapy regimens changed to (1) vindesine (1.8 mg, d1 , d8, d15) + pegaspargase (35 mg, d1-d18 ; from d19 the dose gradually decreased to zero until d25) and (2) cladribine (9 mg, d1-d5) + cytosine arabinoside (90 mg, q12h; d1-d5) and (3) cyclophosphamide (890 mg, d1) + cytarabine (9 mg, d1-d5) + 6-mercaptopurine (67 mg, d1-d7); the three regimens were implemented in turn.

#### Case 3

An 11-year-old boy was referred for examination of a swelling and mass on the left side of his back. The initial diagnosis in a local hospital was lymphadenitis (4 months prior). The involved skin appeared purple and mass continued to grow without pain. One month later he developed a mass in the left axilla with pain, and the mobility of his left upper limb was affected. Drainage and systemic antibiotics were used, but with no improvement. Three days after drainage, the patient developed high fever dyspnea, with swelling of the left shoulder and arm. CT scan showed a back mass (Fig. 3A). Histopathologic evaluation of a lesional skin biopsy showed an infiltrate of atypical lymphoid cells in the superficial and deep dermis (Fig. 3B). Atypical lymphoid cells were positive for CD4, CD8, CD16, CD45, and CD56. He was diagnosed as anaplastic large cell T-cell lymphoma, respiratory failure, and pleural effusion. His parents refused chemotherapy, with symptomatic treatment only, and the patient died.

#### Case 4

A 9-year-old girl was referred for examination of swelling on her left buttock (Fig. 4A). The initial diagnosis was fever which was made in a local hospital 1 month before admitted to our hospital. Systemic antibiotic and dexamethasone were used, but the symptoms persisted. Skin ulceration occurred on the swollen region, but without pain or loss of mobility of the hip joint. Ultrasonography of her left buttock showed apparent swelling and soft tissue thickening by 31mm. Histopathologic evaluation of a lesional skin biopsy showed a panniculitis-like infiltration of lymphocytes and histocytes (Fig. 4B), atypical lymphoid cells were positive for vimentin, CD3, CD20, S100, CD30, CD8 and Ki-67 (80%). An inguinal lymph node biopsy showed cortex hyperplasia and infiltration of lymphocytes and histocytes. Atypical lymphoid cells were positive for vimentin, CD3, CD20, CD1a, S100, CD30, EMA, CD68, and Ki-67 (30%). She was diagnosed as panniculitislike T-cell lymphoma. The chemotherapy agents for her were: (1) vindesine (3 mg, d1 , d8, d15, d22) + prednisone (55 mg, d0d21) + cyclophosphamide (960 mg, d1; 240 mg, d2-d4) + adriamycin (24 mg, d2-d3) + cytosine arabinoside (1.2 g, d4-d5) and (2)ifosfamide (1.3 g, d1-d5) + etoposide (65 mg, d3-d5) + methotrexate (560 mg, d1) + vindesine (3 mg, d1) + prednisone (60 mg, d1-d7); the two regimens applied alternately. So far, she has received 3 doses of chemotherapy.

# Discussion

Primary CL commonly presents with cutaneous masses or nodules in either single or multiple sites, with varying sizes.<sup>4, 5</sup> Primary CL is rare in children and often misdiagnosed. In this report, we presented four cases of primary CL with skin lesions, including three cases of T-cell lymphoma and one case of B-cell lymphoma. All cases were referred for examination of swellings in the skin of different body area. In contrary to the reported typical symptoms of primary CL, swelling and changes in skin color were the initial symptoms in all cases. The initial diagnoses of these children in local hospitals were rash, abscess, lymphadenitis, and fever, respectively. All four patients were diagnosed as primary CL by histopathologic examination in our hospital. The diagnosis of primary CL depends on skin biopsy, disease progression, and expression of characteristic cell-related proteins, such as CD4, CD8, CD30, etc. However, studies had reported that different patients or subtypes showed remarkable variability in the expression of different markers.6, 7

Although a number of studies of CL in the adult population have been performed, limited reports were available in pediatric population. An early report from Italy summarized 69 pediatric CL cases, including 62 with primary CL and 7 with secondary CL. Among those pediatric cases, 51 were NK-/T- cell lymphoma, eight were B-cell lymphoma, and three were immature hematopoietic malignancies. Furthermore, another study from Korea reported 41 pediatric cases with CL which diagnosed from 1990 to 2012. Among the 42 pediatric CL cases, 29 were primary CL, and 12 were secondary CL, 31 were NK-/T- cell lymphoma, one was B-cell lymphoma, and nine were immature hematopoietic malignancies. In our reports, three cases were T-cell lymphoma and one case was B-cell lymphoma.

Although primary CL has been added to the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification in 2005, the diagnosis of pediatric primary CL is difficult. Many CL patients diagnosed in adulthood had undiagnosed skin manifestations in childhood.<sup>8</sup> The diagnosis of primary T-cell lymphoma at an early stage is difficult because its clinical and pathological features may be seen in simple skin or inflammatory diseases, without well-defined diagnostic criteria.9 In most cases, it takes an average of 6 years from disease onset until confirmation of the diagnosis.<sup>10</sup> The earliest form and the most common presentation of primary T-cell lymphoma is the patch stage, which consists of sharply demarcated, erythematous scaly lesions.<sup>11</sup> The primary T-cell lymphoma cases presented in this report were characterized by prominent involvement of the epidermis and subcutaneous tissue. However, one case also showed involvement of the upper limb (Case 3), together with a pleural effusion, which has not been described in previous reports.

The standard management for CL includes observation, surgical excision, local radiation, and systemic chemotherapy.<sup>12,13</sup> Patient age, disease stage, treatment accessibility and previous treatment history should be considered for choosing appropriate treatments. The management strategies are mainly to relieve symptoms and improve clinical remission. In this study, 3 patients (Case 1, Case 2 and Case 4) were treated with chemotherapy, and the symptoms were alleviated. Long-term follow up is needed to observe the survival rate of these patients. To date, there is no controlled trial showing a survival benefit from any of the therapies. In the future, reduced-intensity conditioning followed by allogeneic stem cell transplantation may be effective as an alternative treatment<sup>14</sup>, even among pediatric patients. With progression of the primary CL, other clinical features such as fever, wasting, lymphadenopathy, hepatosplenomegaly and loss of mobility are often observed.<sup>15</sup> The diagnosis and treatment of pediatric primary CL need collaboration of pediatric haematopathologists and hematoncologists.

In conclusion, primary CL in children is rare. Early diagnosis, accurate classification and staging are important for guiding appropriate treatment for pediatric primary CL and would improve patients' prognosis.

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