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Primary Follicular Lymphoma of the Testis in Children and Adolescents

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Abstract

This study reports six cases of primary follicular lymphoma of the testis (PFLT) in children and adolescents correlated with clinical presentation, pathologic features, treatment and outcome. All six patients (ages 3 to 16 years, median 4 years) had PFLT grade 3 with disease limited to the testis, completely resected and treated with two courses of chemotherapy (cyclophosphamide, vincristine, prednisone, doxorubicin) (COPAD). Event-free survival was 100% (follow-up: median 73 months, mean 53 months, range 6 to 96 months). In conclusion, clinical outcome in children and adolescents with PFLT is excellent with treatment including complete surgical resection and two courses of COPAD.

Keywords

lymphoma B-cell; lymphoma follicular; testis; child; adolescence

INTRODUCTION

Primary non-Hodgkin lymphoma (NHL) of the testis is uncommon representing less than 10% of testicular neoplasms, and 1% of NHLs. It occurs in mostly in older patients as diffuse large B-cell lymphoma (DLBCL) with localized disease. Survival is poor with intensive chemotherapy regimens, even in localized disease.[1]

Primary NHL of the testis is rare in young patients with few reports describing Burkitt/Burkitt-like lymphoma,[2–3] DLBCL,[4] pre-B lymphoblastic lymphoma,[5] and follicular lymphoma (FL).[6–11]

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This report includes the clinical presentation, pathologic features, treatment and outcome of six children and adolescents with primary follicular lymphoma of the testis (PFLT), along with a review of the literature.

MATERIALS AND METHODS

Patient Selection

Eligibility criteria including pretreatment evaluation for Children's Cancer Group (CCG) treatment protocol CCG-5961 as part of the international cooperative protocol FAB/LMB96 Treatment of Mature B-Cell Lymphoma/Leukemia: SFOP LMB96/CCG-5961/UKCCSG NHL 9600 have been previously described.[12] The participating institutions obtained appropriate institutional review board approval of the protocol and informed consent for treatment for all patients.

Pathology Evaluation

Central pathology review including morphologic and immunophenotypic evaluation was performed as described previously.[12] There was not sufficient material available to perform additional immunophenotyping or molecular genetic studies.

Cytogenetic Evaluation

Central cytogenetics review of institution G-banded karyotypes was performed on two original karyotypes of each abnormal clone, or two karyotypes of metaphase cells for each normal case. There was not sufficient material available to perform additional fluorescence in situ hybridization or other molecular cytogenetics studies.

Therapy

Patients were uniformly treated with a chemotherapy regimen of two courses of cyclophoshamide, vincristine, prednisone, doxorubicin (COPAD) without intrathecal chemotherapy.[12]

Survival Analysis

The primary endpoint for analysis was event-free survival (EFS), defined as the time from the start of chemotherapy to any event (death, relapse, progression, second malignant neoplasm), or to last follow-up contact for patients without an event. EFS was estimated with the Kaplan-Meier method.

RESULTS

Case Selection

Among 480 cases of mature B-cell lymphoma/leukemia that completed central pathology review with a diagnosis eligible for CCG-5961, 144 (30%) were DLBCL including six (1.3%) of PFLT. All cases of PFLT contained diffuse areas classified as DLBCL eligible for CCG-5961. There were no cases of Burkitt lymphoma, Burkitt-like lymphoma, or pure DLBCL as a primary NHL of the testis. Among the 480 cases of mature B-cell lymphoma/leukemia, the ethnic origin included: White 356, Hispanic 40, Black 29, Other 22, Indian subcontinent 7, Middle East 7, Oriental 7, North Africa 4, Unknown 3, Caribbean 2, Filipino 2, Far East 1. The ethnic origin of the 144 cases of DLBCL included: White 102, Black 13, Hispanic 11, Other 7, Indian subcontinent 2, Middle East 2, North Africa 2, Oriental 2, Caribbean 1, Filipino 1, Unknown 1.

Clinical Presentation

Patient characteristics are summarized in Table 1 (patients 1 to 6) including age (range 3 to 16 years, median 4 years). Ethnic origin of these six patients included: Hispanic 2, White 2, Indian subcontinent 1, and Other 1. Lactate dehydrogenase was within normal limit in four patients, and mildly increased in two patients (< 20% above institution upper normal limit). Surgical treatment consisted of testis biopsy followed by orchiectomy in one patient, and orchiectomy in five patients. Clinical examination, bone marrow and cerebrospinal fluid examination, and radiology studies (chest x-ray, abdominal ultrasound, computed tomography/magnetic resonance imaging) demonstrated no other sites of disease. All patients were classified as stage I with completely resected disease.

Pathologic Features

All cases contained effacement of tissue architecture or infiltration between seminiferous tubules in a nodular or follicular pattern of large lymphocytes (centroblasts) with some small cleaved lymphocytes (centrocytes). Minor portions contained a diffuse component classified as DLBCL. In the Revised European-American Lymphoma Classification,[13] these cases are follicle center lymphoma, follicular, grade III (3). In the World Health Organization Classification,[14] these cases are FL grade 3A with DLBCL. All cases had portions with prominent fibrosis often involving the capsule, and no necrosis. Immunophenotyping (patients 2 to 6) demonstrated a B-cell phenotype (CD20 and CD79a positive; CD3, CD45RO, and TDT negative) with some immunoreactivity for CD30 (scattered cells in patient 5, many cells in patient 6).

Cytogenetic Studies

One case (patient 3) had a tumor specimen with a normal karyotype. There were no karyotype results from tumor in five cases.

Response Evaluation

All patients were in complete remission after unilateral orchiectomy.

Survival

All patients were alive with no evidence of disease at last follow-up contact, and no events (Table 1, patients 1 to 6). EFS was 100% (follow-up interval: median 73 months, mean 53 months, range 6 to 96 months).

DISCUSSION

This report describes the largest series of PFLT in children and adolescents, with uniform therapy on a clinical trial. All six patients had disease limited to the testis completely resected by unilateral orchiectomy followed by chemotherapy of two courses of COPAD. There was no disease relapse during long-term follow-up. The clinical and pathologic features of these patients represent a unique subset among pediatric NHLs.

Previous cases of pediatric PFLT have similar clinical and pathologic features to this report (Table 1, patients 1, 2, 7 to 15).[6–11] The patients had age range from 3 to 11 years. All patients had a primary testis tumor with localized disease, consisting of a FL grade 3 with most cases including a portion classified as DLBCL. Treatment usually included chemotherapy utilizing a variety of regimens, along with one patient treated by surgical excision alone. All patients were alive with no evidence of disease and no disease relapse during follow-up (median 19 months, range 7 to 59 months). PFLT including a portion classified as DLBCL does not indicate an adverse outcome.

When lymphoma is suspected, the data presented here support an aggressive surgical approach with testis biopsy and orchiectomy for disease limited to the testis. While all cases in this series were unilateral, biopsy followed by chemotherapy might be more appropriate in the case of bilateral testicular involvement.

The biologic features of pediatric PFLT have some differences from follicular lymphomas in adults. [6–11] Immunophenotyping studies demonstrated a B-cell phenotype (CD20 positive) with expression of CD10 and bcl6 proteins. However, bcl2 protein was not detected. Molecular genetic studies demonstrated immunoglobulin heavy chain (*IGH*) gene rearrangements in most cases, with no rearrangement involving the *BCL2* gene. *BCL6* gene rearrangement was reported in one case. The presence of CD20, CD10, and BCL6 proteins along with IGH gene rearrangement is expected for FL, but the absence of bcl2 protein and *BCL2* gene rearrangement is unusual in adults.[14]

FLs are rare among childhood NHLs with clinical presentation usually involving the head and neck region as localized disease. The pathologic features include different histologic grades, mostly grade 3 and some grade 2, with few grade 1. Pediatric follicular lymphomas usually express CD10 and bcl6 proteins without bcl2 protein and *BCL2* gene rearrangement, and have an excellent outcome. Most were treated with chemotherapy, but some were treated with surgical excision alone. These features distinguish pediatric FL from adult FL, and have led to recognition of pediatric FL as a distinct variant in the World Health Organization Classification.[14–15]

Primary NHL of the testis in adults is most frequently DLBCL [1,4] of the non-germinal center B-cell like (GCB) group.[16] It is most often localized disease, but survival is poor even with intensive chemotherapy regimens (Ann Arbor Stage I less than 60% overall survival at 5 years). Recurrent disease often involves other extranodal sites such as the central nervous system (CNS) (13% CNS relapse in initial Ann Arbor Stage I disease).[1] In pediatric PFLT, the excellent outcome with low intensity treatment of short duration without intrathecal chemotherapy is a distinctive difference from adult primary DLBCL of the testis.

Pediatric patients with localized mature B-cell NHL still have excellent survival as chemotherapy has been reduced from earlier regimens, with elimination of intrathecal chemotherapy and radiation.[12] Further reduction of chemotherapy such as elimination of cyclophosphamide, [12] or new agents such as monoclonal antibodies (i.e. Rituximab, Children's Oncology Group ANHL01P1),[17] may reduce risk of toxicity and late effects without reducing survival. For children with completely resected FL, some patients have been successfully treated with surgery alone, suggesting there is no occult systemic disease. This observation contributed to the management of one pediatric PFLT by orchiectomy alone, followed by a 30 month interval without recurrence.[11] This suggests that further reduction or elimination of chemotherapy may be possible in pediatric PFLT.

Due to its rare occurrence, future advances in the management of PFLT in children and adolescents may be achieved through enrollment of patients on the Children's Oncology Group ANHL04B1 Rare And Cutaneous Non-Hodgkin Lymphoma Registry.[18] This may encourage further biology studies such as cytogenetic or gene expression studies that can extend the current findings and identify potential new therapeutic targets.[19] Further advances in treatment strategies for PFLT may require future international cooperative protocols.[18,20]

In conclusion, PFLT in children and adolescents is a unique subset of pediatric NHL. It occurs at an unusual extranodal site with localized disease limited to the testis. The clinical outcome is excellent with treatment including complete surgical resection and short duration chemotherapy of two courses of COPAD.

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TABLE 1

Patient Characteristics in Children and Adolescents with Primary Follicular Lymphoma of the Testis.

Patient	Age (years)	Site	Size (cm)	Histology	Chemotherapy	EFS (months)
1[†]	3	L	2.8[†]	F&D	COPAD	27+
2[†]	4	R	2.3[†]	F&D	COPAD	96+
3	4	L	3.8	F&D	COPAD	73+
4	4	R	3.0	F&D	COPAD	6+
5	11	L	3.0	F&D	COPAD	74+
6	16	R	8.0	F&D	COPAD	44+
7 *f*	3	L	3.0	F	None	30+
8 *d*	4	L	2.0	F&D	BFM 86	26+
9 *e*	4	R	3.0	F	CHOP	7+
10 *b*	5	R	4.0	F	COMP	24+
11 *e*	5	R	NA	F&D	CHOP	41+
12 *c*	6	R	3.0	F&D	CHOP	7+
13 *a*	8	L	2.0	F&D	DCOMP	8+
14 *b*	10	L	4.0	F	Orange	19+
15 *e*	11	L	NA	F&D	CHOP	59+

Abbreviations: BFM 86, cyclophosphamide prednisone dexamethasone ifosfamide methotrexate cytarabine prednisolone teniposide doxorubicin; COPAD, cyclophoshamide, vincristine, prednisone, doxorubicin; CHOP, cyclophosphamide doxorubicin vincristine prednisone; COMP, cyclophosphamide vincristine methotrexate prednisone; D, diffuse; DCOMP, daunomycin COMP; EFS, event-free survival; F, follicular; L, left; NA, not available; NED, no evidence of disease; Orange, cyclophosphamide mesna doxorubicin vincristine cytosine arabinoside methotrexate prednisone methylprednisolone hydrocortisone; R, right; +, continuing EFS at the time of follow-up.

[†]Previously reported EFS 18 months. b

*a*Moertel et al.[6]

*b*Finn et al.[7]

*c*Lu et al.[8]

*d*Pileri et al.[9]

*e*Pakzad et al.[10]

$f_{\text{Heller et al.}}$[11]