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Characteristics and Outcome of Pediatric Non-Hodgkin Lymphoma Patients With Ovarian Infiltration at Presentation

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Background. Ovarian infiltration in pediatric non-Hodgkin lymphoma (NHL) at presentation is rare and information on outcome is scarce and mainly based on case reports and small series. ***Procedure.*** Evaluation of clinical characteristics and outcome of ovarian infiltrated pediatric NHL cases of a single center, and an extensive review of the all cases reported so far in literature. ***Results.*** At presentation, 6/60 female NHL cases of our center had ovarian infiltration, and combining these cases with earlier case reports, a total of 42 cases were identified. Median age at presentation was 10.9 years (range 0–18), and all but one had a B-cell immunophenotype, with 32/42 cases being classified as Burkitt. Bilateral involvement was reported in 26/41 cases, of which 22 were bilaterally ovariectomized as first treatment. All cases were treated with chemotherapy. Relapses were reported in 9/36 and death in 16/36. After follow-up in our center (median 13.4 years), in 2 cases anti-Müllerian hormone (AMH) values were available (2.1 and 0.9 μg/L), in non-ovarian cases median 2.2 μg/L. ***Conclusions.*** We conclude that in case of ovarian tumors with negative markers, NHL should be considered in order to avoid unnecessary surgery. Pediatr Blood Cancer 2013;60:2054–2059. © 2013 Wiley Periodicals, Inc.

Key words: gonadal function; non-Hodgkin lymphoma; pediatric; ovarian infiltration

INTRODUCTION

Lymphomas account for 10–15% of all pediatric cancers of which the non-Hodgkin lymphoma (NHL) group represents 60% [1]. The most common sites of presentation of NHL are the mediastinum, neck, and abdomen [2]. At initial presentation, lymphomas rarely involve the ovaries, in children as well as in adults. The scarce information on clinical presentation of ovarian infiltrated pediatric NHL is mainly based on case reports and small series combining ovarian infiltration in adults and children, and the frequency based on cohort studies is unknown [3,4]. In addition, it is unknown what the influence is on gonadal function later in life. In the current report, we present (1) a retrospective single center analysis of the frequency, clinical features, and outcomes of ovarian infiltration of NHL at presentation of girls diagnosed with NHL in our institution, and (2) an extensive review of the clinical characteristics and survival of all well-documented ovarian infiltrating NHL cases in childhood reported in the literature.

METHODS

Single Center Data Analysis

From 1966 to 2012, 160 consecutive pediatric non-Hodgkin lymphoma cases were diagnosed in the Pediatric Oncology/Hematology department of the Erasmus MC-Sophia's Children's Hospital, of which all 60 girls were included in this retrospective survey. Medical records were reviewed for clinical characteristics, that is, sex, age at diagnosis, presenting symptoms, tumor characteristics, subtype (radiological, histopathological, and immunophenotypical reports), disease stage (computed tomography or ultrasound) at baseline, upfront chemotherapy, and other types of treatment (ovariectomy, other surgery, abdominal radiotherapy, and stem cell transplantation), as well as outcome parameters. The diagnosis of ovarian infiltration of NHL was derived by findings on abdominal ultrasound, which is together with CT, MRI, and PET scans a common diagnostic tool in the staging procedure for NHL in children, and confirmed in 4/6 by CT/MRI scan. In two cases (diagnosed in 1982 and 1990), only ultrasound was performed.

Serum AMH Level Assessment

Serum anti-Müllerian hormone (AMH) level was used as a proxy for gonadal function in our female childhood cancer survivors (CCS) [5–8]. Serum AMH levels were measured using an in-house double-antibody enzyme-linked immunosorbent assay; intra- and interassay coefficients of variance (CVs) were $<10\%$ and $<5\%$, respectively [9,10], and compared to healthy Dutch women. These women were proven fertile or had regular menstrual cycles [11].

Literature Review

We conducted searches in the electronic databases PubMed, Embase, Medline, Cochrane, and Web of Science in January 2012, using the following key words and their synonyms: ovary, non-Hodgkin lymphoma, child. Studies were eligible for selection if NHL cases were individually well-documented; aged less than 19 years at diagnosis; NHL at baseline; ovarian infiltration at presentation; the article was published in a peer reviewed scientific

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journal written in the English or Dutch language. After removing the duplicates, the author screened titles and abstracts to select eligible studies. Full text papers were obtained of the selected papers, and were excluded by the author if studies did not meet the inclusion criteria. The complete search strategy is available on request.

RESULTS

Descriptives of Single Center Study

Six of the 60 girls (10%) diagnosed with NHL in our center had ovarian infiltration at diagnosis (Table I). The median age at diagnosis of these cases was 10.5 years (range 3.1–15.7). All six

TABLE I. Patient Characteristics at Baseline in the Single Center Cohort

	Ovarian infiltration	No ovarian infiltration	Total
N total	6	54	60
Median age at diagnosis (in years)	10.5 (3.1–15.7)	9.1 (0.4–16.4)	9.1 (0.4–16.4)
Presenting symptoms/physical exam			
General (fever, fatigue, and weight loss)	2 (33.3)	25 (46.3)	27 (45.0)
Abdominal symptoms	5 (83.3)	19 (35.2)	24 (40)
B-symptoms	1 (16.7)	4 (7.4)	5 (8.3)
Palpable nodes	1 (16.7)	16 (29.6)	17 (28.3)
Abdominal mass	4 (66.7)	24 (44.4)	28 (46.7)
Ascites	1 (16.7)	1 (1.9)	2 (3.3)
Hepatosplenomegaly	1 (16.7)	7 (13.0)	8 (13.3)
Pleural fluid	0	4 (7.4)	4 (6.7)
Subtype			
Burkitt lymphoma	6 (100.0)	11 (20.4)	17 (28.3)
DLBCL	0	7 (13.0)	7 (11.7)
T-LBL	0	17 (31.5)	17 (28.3)
Precursor B-NHL	0	4 (7.4)	4 (6.7)
ALCL	0	13 (24.1)	13 (21.7)
Unclassified	0	2 (3.7)	2 (3.3)
Organ infiltration			
Ovary	6	0	6 (10.0)
Kidney	2 (33.3)	5 (9.3)	7 (11.7)
Liver	1 (16.7)	2 (3.7)	3 (5.0)
Spleen	0	2 (3.7)	2 (3.3)
Pancreas	0	1 (1.9)	1 (1.7)
Mesentery	0	4 (7.4)	4 (6.7)
Intra-abdominal	0	5 (9.3)	5 (8.3)
Mediastinum	1 (16.7)	19 (35.2)	20 (33.3)
Lymph noduli	1 (16.7)	24 (44.4)	25 (41.7)
Bone marrow	0	8 (14.8)	8 (13.3)
CNS	0	4 (7.4)	4 (6.7)
Skin	0	4 (7.4)	4 (6.7)
Other	0	3 (5.6)	3 (5.0)
Stage			
Stage I	0	12 (22.2)	12 (20.0)
Stage II	0	9 (16.7)	9 (15.0)
Stage III	6 (100.0)	16 (29.6)	22 (36.7)
Stage IV	0	17 (31.5)	17 (28.3)
Other therapy			
Abdominal radiotherapy	1 (16.7)	0 (0.0)	1 (1.7)
Stem cell transplantation	0	3 (5.6)	3 (5.0)
Ovariectomy	3 (50.0)¶	2 (3.7)	5 (8.3)
Ileum resection	0	5 (9.3)	5 (8.3)
Event			
Relapse	0	11 (20.4)	11 (18.3)
Death	2 (33.3)	14 (25.9)	16 (26.7)
Median time diagnosis—relapse (in months)	—	11 6.5 (2.6–12.1)	11 6.5 (2.6–12.1)
Median time diagnosis—death (in months)	2 6.9 (6.4–9.0)	13 11.0 (6.4–140.1)	15 9.6 (4.8–140.1
Median time relapse—death (in months)	2 2.1 (1.0–3.1)	10 4.3 (0.3–137.1)	12 3.9 (0.3–137.1)

Data is presented in median (range) of N (%). N, number; DLBCL, diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; Precursor B-NHL, pre-B-cell lymphoblastic lymphoma; ALCL, anaplastic large cell lymphoma; CNS, central nervous system; AMH, anti-Müllerian hormone. ¶, of which two were unilateral ovariectomy and one was bilateral at diagnosis in 1982.

(four unilateral, two bilateral) were stage III, according to the Murphy's staging system [12], and were immunophenotyped as B-cell (Burkitt type) NHL. The most common presenting symptoms were abdominal pain and/or mass (n = 6/6), one case was complicated by hydronephrosis (n = 1/6). Alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (b-HCG) were within normal range in all six cases. All patients were treated with multi-agent chemotherapy. One patient had upfront bilateral ovariectomy, which was performed in 1982 because of "malignant appearance" during laparotomy at presentation according to the surgical reports. Two patients were treated with unilateral ovariectomy, the first for debulking of the tumor and the second because of incomplete response to chemotherapy. Abdominal radiotherapy was administered in one patient, 7 months post-diagnosis due to progression of disease 7 months into therapy. None received stem cell transplantation (SCT). Two out of six patients had disease progression within 6 months from diagnosis and eventually died due to progressive and incurable disease. The characteristics and outcome of the ovarian infiltrated as well as the other NHL cases are depicted in Table I.

In the long-term survivors (n = 44), serum AMH levels were available in 25 cases, including 3/6 cases with ovarian infiltration. Two of these three cases, aged 14.8 and 16.3 years at time of screening, had been treated with chemotherapy only (AMH levels 2.1 and 0.9 μg/L), and one case aged 28.4 years at screening had been treated with a bilateral ovariectomy (AMH level <0.1 μg/L). Follow-up times were respectively 1.3, 7.3, and 24.3 years. None of these three women underwent abdominal radiotherapy. The 22 female CCS without ovarian infiltration had a median serum AMH level of 2.2 μg/L (range <0.1–8.1) at a median follow-up time of 13.4 years (range 0.3–27.7) and a median age of 22.9 years (range 4.5–40.3) at screening. Figure 1 shows the serum AMH levels of our single center female NHL CCS, in comparison with serum AMH levels of healthy Dutch controls [11].

Literature Review of Ovarian Infiltrated NHL

The combined search resulted in 537 articles. After screening the titles and abstracts, 64 articles met the inclusion criteria and were retrieved for further assessment. Twenty manuscripts were selected based on inclusion and exclusion criteria. Of the selected articles, a cross-reference of related articles, references and citing articles was performed. This yielded no further manuscripts for inclusion. This search resulted in 36 well documented cases of childhood ovarian infiltrated NHL, enabling a review of clinical characteristics and outcome of 42 cases in total (Table II). The median age was 10.9 years (range 0.9–18.0) at presentation. Except for one incidental finding, all cases presented with abdominal pain and/or abdominal mass. Ascites at presentation was found in 9/42 cases, fever in 10/42 cases, and 5/42 cases had respiratory symptoms. In 42 cases the immunophenotype was described. All but one had a B-cell immunophenotype, with 32/42 cases being classified as Burkitt and 9/42 as B-NHL. One patient was diagnosed with ALCL with a t(2;5) fusion gene, with unavailable specific information on the immunophenotype.

Bilateral ovarian involvement at diagnosis was described in 26/41 cases (63.4%). In one case, the side of ovarian infiltration was not specified. Concomitant infiltration of other organs than the ovary was described in 22/42 cases, and included other intra-abdominal sites (uterine tubes, uterus, small intestine, appendix, mesentery, retroperitoneum, liver and the stomach; n = 2/42), orbita (n = 1/42) and chest (mediastinal enlargement and pleural effusion; n = 6/42). Data on disease stage, CNS and BM involvement at presentation were available for respectively 34, 32, and 36 cases. Based on the Murphy's staging system 4/34 stage II and 29/34 cases were stage III. Only one case was diagnosed with stage IV due to CNS involvement and none had BM infiltration (Table II).

Chemotherapy was administered in 38/42 cases, ovariectomy in 34/41 and abdominal radiotherapy in 6/41 cases. Upfront ovariectomy was performed in 31/41 cases (9 were performed unilateral and the other 22 bilateral). Upfront chemotherapy was administered in 10/41 and one case was initially treated with abdominal radiotherapy. Two other cases were treated with unilateral ovariectomy after failure or incomplete response to chemotherapy. Other types of surgery because of complications or infiltration of the disease, such as hemicolectomy, cystectomy, hysterectomy, appendectomy, and omentectomy, were described in 14/41 cases (Fig. 2). 36/42 cases had available data on clinical outcome. Relapses occurred in 9/36 of the well-described cases; all but one resulted in death. Eight other patients were reported to die of extreme toxicity, that is, extreme progressive cachexia, complete intestinal obstruction, and sepsis.

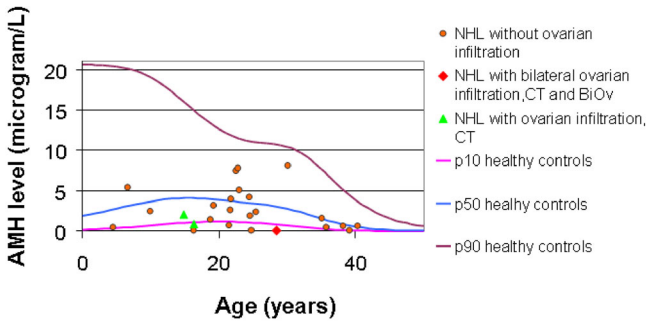

Fig. 1. Serum AMH levels in NHL survivors in single-centre cohort. Anti-Müllerian hormone levels in NHL patients as compared to the p10, p50, and p90 in 250 healthy controls [11]. NHL, non-Hodgkin lymphoma; CT, chemotherapy; BiOv, bilateral ovariectomy.

DISCUSSION

NHL in children usually presents with lymph node involvement with consequent symptoms and to a lesser extend with organ infiltration. The current report indicates that infiltration of the ovaries at presentation of pediatric NHL is rare, which is similar to what has been reported in adults [13]. Therefore, specific clinical characteristics are difficult to describe. From the observation of the 42 reviewed cases including our own particular cohort, all pediatric cases presented with abdominal pain and/or abdominal mass, which again is comparable with the presentation as described in adult cases [3,14].

Most pediatric cases showed a B-cell NHL immunophenotype, of which the majority had a Burkitt type, which may be a reflection of the most common lymphoma found in children [15]. This is in line with reported adult ovarian infiltrated NHL cases, where mainly diffuse large B-cell lymphoma (DLBCL) is found, followed by Burkitt lymphoma [3,14,16]. Nevertheless, it may also stress the specific tendency of homing of malignant B-cell NHL cells rather

TABLE II. Clinical Features of Cases of Pediatric Ovarian Non-Hodgkin Lymphoma

			Symptoms and examination at presentation							Ovarian infiltration		Other sites of involvement at diagnosis					Treatment				Outcome			CCR postDx
Refs.	N	Age at Dx (yr)	Fever	Abd.	Re.	Abd. mass	Ascites	Subtype	Stage	Uni	Bi	Intr-abd.	CNS	BM	Orbita	Thor	Uni-ov.	Bi-ov.	CT	Abd RT	Rel.	D	D (mo)	(mo)
Seed [21]	1	15	0	1	0	1	0	BL	III	1	0	1	0	0	0	0	1	0	1	1	0	1	4	
Jamra [22]	1	12	1	0	0	1	0	BL	NA	0	1	0	0	0	0	0	0	0	1	0	0	0		NA
Bluming [23]	1	4	0	1	0	1	0	BL	NA	0	1	0	NA	NA	0	0	1	0	1	0	0	0		
Pickleman [24]	1	7	1	1	1	1	0	BL	III	0	1	0	0	0	0	0	0	1	1	0	0	1	7	
Nkrumah [25]	5	10	0	0	0	5/5	0	5x BL	4x III, 1x IV	2/5	3/5	1/5	1/5	0	0	0	2/5	3/5	5 × 1	0	3/5	4/5	3, 8, 18.5, 28	>26
Aggio [26]	1	4	0	1	0	1	0	BL	NA	0	1	1	NA	0	0	0	0	1	1	0	0	1	0.5	
Kuramoto [27]	1	15	0	1	0	1	1	BL	III	1	0	1	NA	NA	1	0	1	0	1	0	0	1	1.5	
Piura [28]	1	16	0	1	0	1	0	B-NHL	NA	0	1	0	NA	0	0	0	0	1	1	1	0	0		>120
Weekes [29]	1	15	1	1	0	1	1	BL	III	0	1	1	0	0	0	1	0	1	1	0	NA	NA		
Monterroso [3]	12	12	1/12	3/12	1/12	10/12	2/12	9 BL, 3 B-NHL	3x II, 9x III,	4/11[a]	7/11[a]	11/12	0/12	1/12	0	3/12	2/11	8/11	9/11	3/11	6/9	5/9	1, 6, 7, 10, 15	53, 72, 105, 197
Creatsas [30]	2	16	1/2	2/2	0	2/2	0	BL, N-NHL	II, III	1/2	1/2	0	0	0	0	0	1/2	1/2	2/2	0	0	0		36, 60
Mitsumori [31]	1	12	0	1	0	1	0	B-NHL	NA	0	1	0	NA	NA	0	0	0	0	1	0	0	0		
Turken [32]	1	0.9	0	0	0	1	0	NHL	III	0	1	0	NA	0	0	0	0	1	1	0	0	0		8
Azizoglu [17]	1	16	0	1	0	1	0	BL	III	0	1	0	NA	NA	0	0	0	1	0	0	NA	NA		
Eren [33]	1	4.5	0	1	0	1	1	BL	NA	0	1	1	NA	NA	0	0	0	1	1	0	0	1	0.5	
Koksal [34]	1	9	0	1	1	1	1	B-NHL	III	1	0	0	0	0	0	1	1	0	1	0	0	0		6
Ray [35]	1	8	0	1	0	1	0	B-NHL	NA	0	1	0	NA	NA	0	0	0	1	1	0	NA	NA		
Chong [18]	1	14	1	1	1	1	1	ALCL	III	1	0	1	0	0	0	1	1	0	1	0	0	0		24
Cyriac [36]	1	13	1	1	0	1	1	BL	NA	0	1	0	NA	0	0	0	0	0	1	0	0	0		6
Chakrabarti [37]	1	1.7	1	0	0	1	0	BL	III	0	1	1	0	0	0	0	0	1	1	0	0	0		28
Present report	6	10.5	2/6	6/6	1/6	4/6	1/6	6x BL	6x III	4/6	2/6	3/6	0/6	0	0	1	2/6	1/6	6 × 1	1/6	0	2/6	5, 9	12,24, 84, >25yr
Total	42	10.9	10/42	25/42	5/42	38/42	9/42	—	—	15/41	26/41	22/42	1/32	1/36	1/42	6/42	12/41	22/41	38/42	6/41	9/36	16/36		

Data is presented in median or N. N, number; Dx, diagnosis; Abd, abdominal symptoms; re, respiratory symptoms; BL, Burkitt lymphoma; B-NHL, B-non-Hodgkin lymphoma; ALCL, anaplastic large cell lymphoma; Uni, unilateral; bi, bilateral; intra-abd, intra-abdominal; CNS, central nervous system; BM, bone marrow; thor, thoracal; CT, chemotherapy; ov, ovariectomy; RT, radiotherapy; Rel, relapse; D, death; mo, months; yr, year; CCR, complete clinical remission; NA, not available. [a]In one case site not specified.

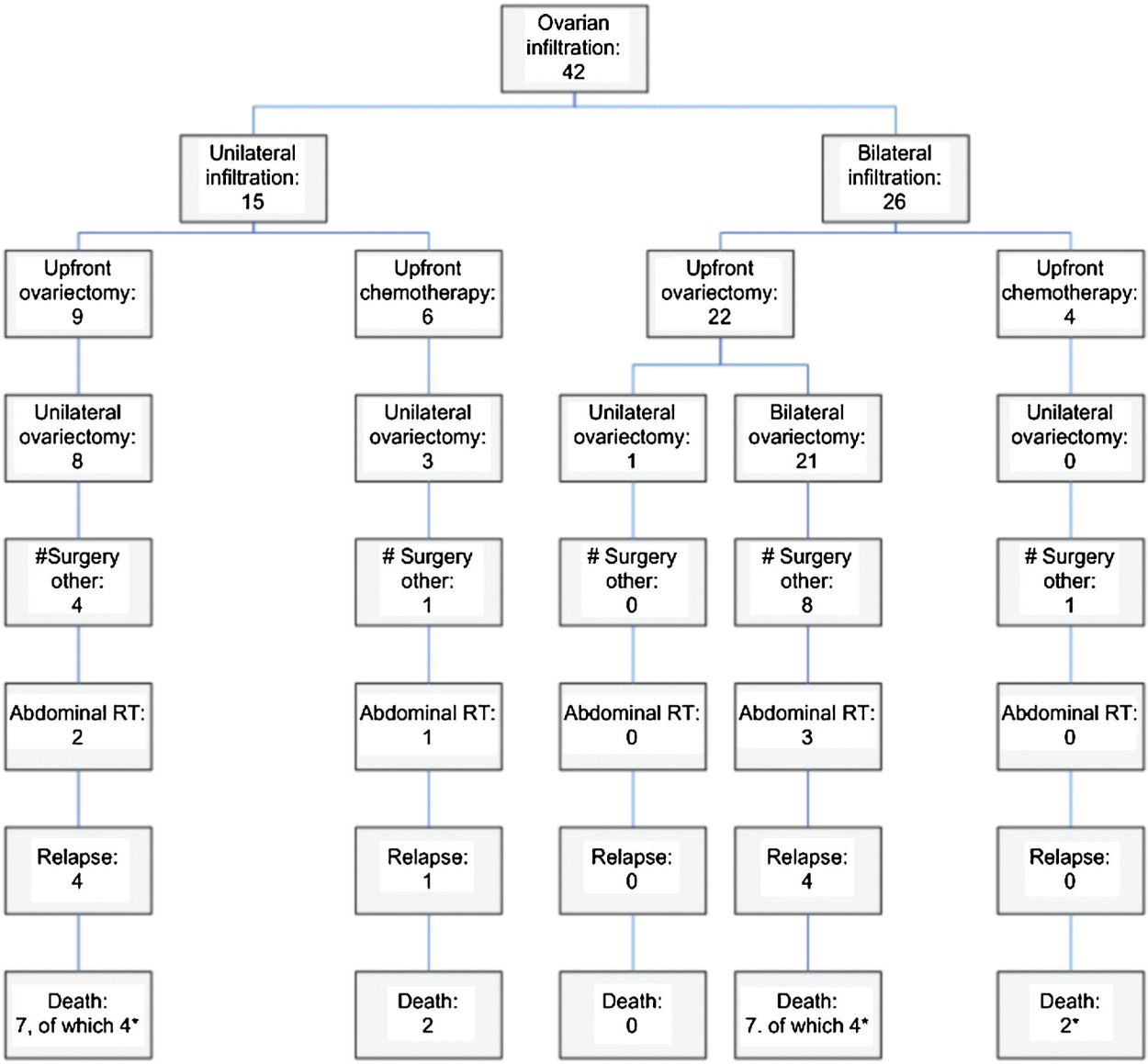

Fig. 2. Treatment algorithm of pediatric ovarian infiltrated cases. In one case, ovarian infiltration is not specified in unilateral or bilateral.*Death due to treatment toxicity such as extreme progressive cachexia, complete intestinal obstruction or sepsis. #Other types of surgery performed, such as hemicolectomy, cystectomy, hysterectomy, appendectomy, and omentectomy.

than T-NHL cells to infiltrate ovarian tissue, which suggests that Burkitt lymphomas preferentially involve the ovaries. The explanation of this is unknown. Only three adult primary ovarian ALCL cases have been reported of which two immunophenotypically showed T-cell lineage monoclonality [3,16–18]. The pediatric case that was cytogenetically confirmed as anaplastic large-cell lymphoma (ALCL) was not immunophenotyped.

BM involvement was not, and CNS infiltration was reported only once in the 42 pediatric ovarian infiltrated NHL cases. This could be an illustration of the fact that B-NHL, that infiltrates ovarian tissue, represents a distinct biological entity with a different homing biology. However, in general, BM and CNS involvement in B-cell NHL in children occurs only in approximately 5% and 10%, respectively [19,20], and considering the limited number of patients this finding should be interpreted with caution.

Bilateral ovarian infiltration was reported in over half of the ovarian infiltrated pediatric NHL cases. Upfront ovariectomy was performed in 65% of the pediatric cases, of which strikingly 71% bilateral, even in recent years after improving diagnostic process of NHL, and even after confirming negative gonadal tumor markers. It is important to take into account the year of diagnosis, but even after 2000, the majority of the patients (7/8) have been treated with ovariectomy. Moreover, even in the early seventies authors discussed the upfront ovariectomy as first treatment and advised surgeons to be aware of ovarian infiltration in non-Hodgkin patients since treatment was advised to be predominantly non-operative [24]. As chemotherapy alone is often sufficient to cure NHL in children, these findings urge the need to consider the diagnosis of NHL in such cases, and to perform needle biopsies in a selected subset of children with ovarian tumors that do not reveal positive

tumor markers (AFP and b-HCG), especially in children with bilateral ovarian infiltration. This however points to a diagnostic dilemma, as it should be kept in mind that there is a potential risk of tumor spread when performing needle biopsies in such cases. This risk should be taken into account, but especially given the strong curing potential of intensive chemotherapy, it has to be balanced against the risk of performing an ovariectomy upfront, which can substantially impair gonadal function and fertility as illustrated by the decreased serum AMH level in the bilaterally ovariectomized patients. Subsequent premature loss of ovarian function does have an incredible detrimental impact on a women's general health later on in life.

In conclusion, ovarian infiltration in pediatric NHL is rare, and is predominated by B-NHL phenotype. Considering the current excellent outcome using intensive chemotherapy only, awareness of NHL in case of ovarian tumors with negative tumor markers (AFP and b-HCG) is important in order to avoid unnecessary upfront surgery, especially in case of bilateral ovarian infiltration. Nevertheless, gonadal function should be carefully monitored in all long-term survivors of pediatric NHL, due to the potential risk of post-surgery-, chemo- and radiotherapy-related impairment.

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