Retrospective Study of the Radiological Findings of The Mediastinum After End-of-Treatment for a Mediastinal Lymphomatous Mass in Pediatric Oncology

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1. ABSTRACT

1.1 INTRO Reactive thymic hyperplasia following chemotherapy in children treated for mediastinal lymphoma can be misdiagnosed as tumor relapse. This phenomenon may cause unnecessary imaging or diagnostic procedures.

1.2 OBJECTIVES The main objective of this study was to measure the incidence of reactive thymic hyperplasia following treatment for mediastinal lymphoma in children. The secondary objectives were to describe the radiologic findings which may help differentiate thymic hyperplasia and tumor relapse and to analyse if the finding of a mediastinal mass changed the clinical management of the patient.

1.3 METHODS The medical and radiologic records of 72 pediatric patients who had completed two years of follow-up after treatment for mediastinal lymphoma were reviewed in this retrospective study. The radiologic imaging reports were analysed and the patients were classified depending on whether they developed a mediastinal mass during follow-up or not. If a mass developed, its characteristics were described in order to differentiate between tumor relapse and thymic hyperplasia.

1.4 RESULTS Thirty-nine (54%) patients had developed a mediastinal mass during follow-up. Thirty-five of them had no relapse, and their mass was classified as reactive thymic hyperplasia. Three patients had a mediastinal tumor relapse. In 12/35 (34%) patients having a benign mediastinal mass at follow-up, the clinical management was modified based on the radiological findings.

1.5 CONCLUSION Reactive thymic hyperplasia is a common phenomenon, as it developed in half of our cohort of patients. Some radiological findings, including a triangular shape, well-defined margins and mild homogenous enhancement, oriented towards a rebound thymic hyperplasia.

Keywords: Lymphoma, Rebound Thymic Hyperplasia, Recurrence

2. MAIN TEXT

2.1 INTRODUCTION

Reactive thymic hyperplasia, or rebound thymus, is a well-known phenomenon following chemotherapy in children and young adults with malignancy[1]. While rebound thymus has been described after treatment for many different malignancies such as rhabdosarcoma[2], nephroblastoma[3], sarcoma[4], leukemia[5-6], breast cancer[7] and germinal cell tumors[8], this phenomenon has been more often noted after treatment for lymphomas[5-9-10-11-12]. In children and adolescents in whom the primary lymphoma was located in the mediastinum, a mass appearing in this area, such as a reactive thymic hyperplasia, can be misdiagnosed as a tumor relapse. It can be difficult for clinicians to differentiate between a tumor relapse and reactive thymic hyperplasia, which may cause unnecessary additional imaging and invasive diagnostic procedures, as well as anxiety for the patient and his family.

The exact mechanism of reactive thymic hyperplasia is not well-known[1]. The thymus is a very sensitive organ and has been known to react to many different physiologic stresses such as burns and surgery[13-14]. Experts believe that thymic rebound following malignancy is an immunologic response to chemotherapy[15-16].

Many studies have determined that FDG PET-CT was a good imaging study to diagnose thymic hyperplasia, with characteristics such as triangular shape and a mild FDG uptake[17-18-19]. However, other experts claim true diagnosis of reactive thymic hyperplasia can only be made when a mediastinal biopsy proves it[9-10-11-20]. A mediastinal biopsy is often complex, with the proximity of major blood vessels, and causes anxiety in the patient and his family.

Many case reports of reactive thymic hyperplasia after treatment for mediastinal lymphoma or other malignancies can be found[9-11], but the real incidence of rebound thymus following treatment for mediastinal lymphoma in pediatrics is not well-known. Some studies have shown the incidence of reactive thymic hyperplasia during or after treatment for lymphoma to be around 12-75%[1-12-21-22-23], depending on the population studied.

The main objective of this study was to measure the incidence of reactive thymic hyperplasia following treatment for mediastinal lymphoma in children. The secondary objectives were to describe the radiologic findings which may help differentiate thymic hyperplasia and tumor relapse and to analyse if the finding of a mediastinal mass changed the clinical management of the patient, all in an aim to better describe this phenomenon and reduce unnecessary imaging studies, diagnostic procedures and anxiety.

2.2 METHODS

We conducted a retrospective cohort study. The approval to review medical records was obtained from the institutional ethics board. We obtained data from the archives at the Centre Mère-Enfant Soleil, CHU de Québec-Université Laval.

2.2.1 Patient population

We retrieved the medical records of all patients who had a diagnosis of mediastinal lymphoma between January 1994 and December 2013. Seventy-three records were reviewed. The inclusion criteria were mediastinal lymphomatous mass at diagnosis, maximum age of 18 years old at diagnosis and at least two years of follow-up after end of treatment. The single exclusion criterion was if the clinical and radiologic data were unavailable. Of 73 patients, only 1 was rejected because his medical and radiologic records could not be found. Finally, 72 consecutives patients (47 boys and 25 girls) were enrolled. The characteristics of the patients can be found in *Table 1*.

TABLE 1 – Clinical Features of the Study Population (n=72)

Sex	
Male	47 (65.3%)
Age at diagnosis in years	
Mean [range]	13.2 [1.9-17.9]
Median	14.3
Lymphoma	
Hodgkin	50 (69.4%)
Non-Hodgkin	22 (30.6%)
Histologic type	
Nodular Sclerosis	42 (58.3%)
Lymphoblastic	12 (16.7%)
Mixed Cellularity	6 (8.3%)
Anaplastic Large Cell Lymphoma	4 (5.6%)
Diffuse Large B-Cell	3 (4.2%)
Nodular Lymphocyte Predominant	2 (2.8%)
Burkitt	2 (2.8%)
Lymphocyte-Rich	1 (1.4%)
Stage	
I	0 (0%)
II	26 (36.1%)
III	25 (34.7%)
IV	21 (29.2%)
Chemotherapy cycles	
Mean [range]	4.6 [2-15]
Mediastinal Radiotherapy	
Yes	37 (51.4%)
No	35 (48.6%)

2.2.2 Data collection

The clinical data were collected using the paper record and/or the electronic record of the patients, depending on which was available. We collected information on the characteristics of the patient such as the type of lymphoma, the protocol, and the number of chemotherapy cycles received. We reviewed all the follow-up imagery

reports, and noted if a mediastinal rebound mass was discovered during follow-up. If a mediastinal rebound mass was discovered, we reviewed the description of the mass and the evolution of the patient to lymphoma relapse or rebound thymic hyperplasia. When available, the radiologic imaging was reviewed by the radiology specialist (N. F.) to better describe the mediastinal rebound mass. The follow-up period began when treatment was completed and ended with the last imaging study done for the patient and his last follow-up visit at the time of data collection.

2.2.3 Statistical Analysis

Descriptive analysis includes mean ± standard deviation, range and median, interquartile range for continuous variables, and frequency and percentage for categorical variables. Bivariate tests (Chi2, Fisher exact, Wilcoxon-Mann-Whitney, when appropriate) were used to compare the rebound thymic hyperplasia group with the group without this condition. Afterwards, univariate Cox proportional hazards models were fitted to evaluate the hazards ratio of each variable and see if some clinical characteristics made patients more at risk of developing rebound thymic hyperplasia. Finally, a multivariate Cox proportional hazards model was applied to obtain adjusted hazards ratio with the age, sex and type of lymphoma (Hodgkin or Non-Hodgkin). Proportional hazards assumptions have been verified and were adequate for all Cox models. Statistical analyses were performed using SAS 9.4 Statistical Software (Institute SAS, Cary, NC, USA) with a two-sided significance level set at $p < 0.05$.

2.3 RESULTS

The patients were followed for a mean of 27.7 ± 28.0 months (95% CI 21.1-34.2) and a median of 12.6 months. Of 72 patients reviewed, 39 (54.2%) developed a mediastinal mass at follow-up. Of them, 3 had a mediastinal relapse of their tumor. One patient had a lymphoma relapse located elsewhere than the mediastinum and a benign rebound mediastinal mass. Then, 35 out of the 72 patients (48.6%, 95%CI 37.3%-60%) developed a benign mediastinal mass and were diagnosed with having rebound thymic hyperplasia. Of those 35 patients, 12 were investigated with additional imaging, and 1 had a mediastinal biopsy showing true thymic hyperplasia. The other 23 were followed-up according to the clinician, with no modification to their follow-up because of the mediastinal mass. These results are shown in *Table 2*.

TABLE 2– Results	
No mediastinal rebound mass at follow-up	33/72 (45.8%)
No relapse	31/33 (93.9%)
Lymphoma relapse (other site)	2/33 (6.1%)
Mediastinal rebound mass at follow-up	39/72 (54.2%)
No relapse (thymic hyperplasia only)	35/39 (89.7%)
Mediastinal tumor relapse	3/39 (7.7%)
Lymphoma relapse (other site)	1/39 (2.6%)
Follow-up unmodified	23/35 (65.7%)
Modifications to follow-up	12/35 (34.3%)
Additional PET-CT	6
CT-scan control	6
Additional Gallium Scan	4
Mediastinal biopsy	1

The median and mean follow-up lengths before the discovery of rebound thymic hyperplasia were respectively 3.6 months and 6.2 months (95% CI 4.0-8.4

The clinical description of patients who developed rebound thymic hyperplasia is shown in *Table 3*. None of the patients with rebound thymic hyperplasia had B symptoms at follow-up. Using bivariate analysis, we tried to find out if some characteristics of our study population were associated with more thymic rebound hyperplasia. We found a tendency towards girls having more thymic rebound hyperplasia but the difference was not statistically significant (60.0% vs. 42.6%, p=0.2166).

TABLE 3– Clinical Features of the Patients with and without Rebound Thymic Hyperplasia.			
	Thymic Rebound (n=35)	**No Thymic Rebound (n=37)**	***p* value**
Sex			0.2166
Male	20 (42.6%**)**	27 (57.4%)	
Female	15 (60.0%)	10 (40.0%)	
Age at diagnosis in years			0.1624
Median [IQR]	14.2 (11.9; 15.2)	15.0 (11.8; 16.3)	
Mean ±SD (95% CI) [range]	12.7 ±4.16 (11.25; 14.11) [1.9; 17.7]	13.7 ±4.0 (12.4; 15.0) [4.2; 17.9]	
Time in months post treatment before thymic rebound			
Median [IQR]	3.66 [0.92-31.70]	-	
Mean ±SD (95% CI) [range]	6.2 ±7.0 (3.8; 8.6) [0.9; 31.7]	-	
Lymphoma			1
Hodgkin	24 (48.0%)	26 (52.0%)	
Non-Hodgkin	11 (50.0%)	11 (50.0%)	
Histologic type			0.8046
Nodular Sclerosis	20 (46.5%)	23 (53.5%)	
Lymphoblastic	7 (58.3%)	5 (41.7%)	
Other	8 (47.1%)	9 (52.9%)	
Stage			0.8354
I	0 (0%)	0 (0%)	
II	13 (50.0%)	13 (50.0%)	
III	13 (52.0%)	12 (48.0%)	
IV	9 (42.9%)	12(57.1%)	
Mean amount of Chemotherapy Cycles			0.5688
median [IQR]	4 [3; 5]	4 [4; 6]	
mean ±SD (95% CI) [range]	4.3 ±1.5 (3.7; 4.9) [2.0; 8.0]	4.9 ±2.6 (3.9; 5.9) [3; 15]	
Mediastinal Radiotherapy			0.2381
No	20 (57.1%)	15 (42.9%)	
Yes	15 (40.5%)	22 (59.5%)	

The radiological description of the mediastinal rebound masses is shown in *Table 4*. The details of the masses were not available for all patients, which explains the difference in *total number of patients*. The majority of the rebound thymic hyperplasia were a mass of triangular shape, with well-defined margins and homogenous density. It remained unchanged or minimized at follow-up, but it was noted that 3 patients had an augmentation of the hyperplasia at follow-up, while remaining disease-free. An example of rebound thymic hyperplasia at follow-up is shown in *Figure 1*.

TABLE 4 – Radiological characteristics of Rebound Thymic Hyperplasia		
Shape		*n*=20
	Triangular	14/20 (70%)
	Trapezoid	5/20 (25%)
	Diffuse	1/20 (5%)
Margins		*n*=19
	Well-defined	16/19 (84.2%)
	Ill-Defined	3/19 (15.8%)
Density		*n*=24
	Homogenous	20/24 (83.3%)
	Heterogeneous	4/24 (16.7%)
Enhancement		*n*=19
	Mild	18/19 (94.7%)
	Moderate	1/19 (5.3%)
Relation with Major Blood Vessels		*n*=19
	Displaces	13/19 (68.4%)
	Surrounds	6/19 (31.6%)
	Invades	0/19 (0%)
Evolution of the Mass at Follow-up		*n*=30
	Unchanged	18/30 (60%)
	Diminished	9/30 (30%)
	Augmentation	3/30 (10%)

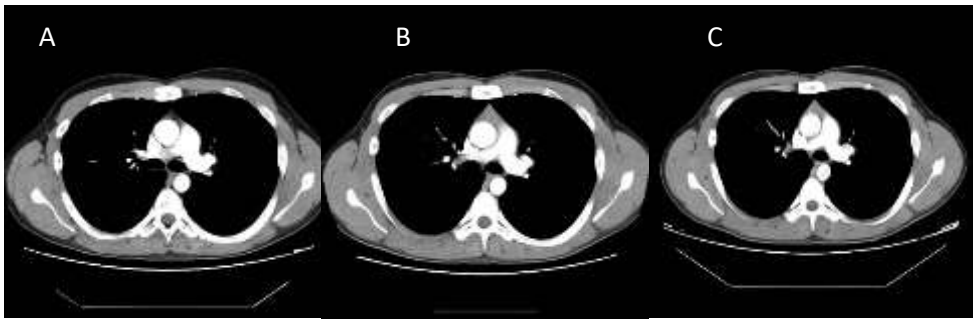

Figure 1. Example of a rebound thymic hyperplasia in a 16 year old male. (A) Normal thymus at end of treatment. (B) Rebound thymic hyperplasia at 5 month follow-up. (C) Slight regression of mass at 1 year follow-up.

The risk factors for developing a rebound thymic hyperplasia are shown in *Table 5*. The age <14 years old was a risk factor in our population (Hazard Ratio (HR) 1.95,

p=.0491). There was a tendency towards girls being more at risk than boys of having a rebound thymic hyperplasia (HR=1.50, *p*=.2399), but this was not statistically significant. In the multivariate Cox model the age stays significant and the gender becomes almost significant.

TABLE 5– Risk Factors for Rebound Thymic Hyperplasia evaluated by Cox proportional hazards models.

	Univariate models			Multivariate model		
Risk Factor	**Hazard Ratio**	**HR 95%CL**	**p value**	**Hazard Ratio**	**HR 95%CL**	**p value**
Age <14 years old	1.95	(1.04; 3.67)	.0491*	2.17	(1.03; 4.56)	0.0417
Sex Female	1.50	(0.76; 2.93)	0.2399	2.19	(0.97; 4.90)	0.0580
Hodgkin Lymphoma	0.73	(0.36; 1.50)	0.3964	0.72	(0.30; 1.74)	0.4627

The characteristics of the 3 patients who had a relapse of their mediastinal tumors are described in *Supplementary Table S1*. Two of them were male. Two had a nodular sclerosis histological type of Hodgkin lymphoma. All 3 of them had significant lymphadenopathy. Two of them had B symptoms. Two of them had a diffuse heterogeneous mass.

2.4 DISCUSSION

This study shows that rebound thymic hyperplasia following treatment for mediastinal lymphoma is relatively common, as almost half of our study population developed it at follow-up. This high prevalence is similar to what has been recently described in the literature for pediatric lymphoma[12], while it is a much rare phenomenon in the adult population, with few cases described[7,24]. The explanation for such a high proportion of pediatric patients developing a rebound mediastinal mass is probably related to the well-known sensibility of the thymus to physiological stress, including surgery, trauma, burns and chemotherapy[13-14]. Treatment with chemotherapy creates an immunologic response which in turn causes the thymus to enlarge, while conserving its physiological and histological proportions[25]. Thymic hyperplasia is therefore a benign condition linked to the immune recovery following end of treatment. Some authors have even found rebound thymic hyperplasia to be a positive prognostic factor in a pediatric population with lymphoma following chemotherapy treatment[26].

The high prevalence in our study population can also be partially explained by the fact that the initial lymphoma was located in the mediastinum. The follow-up therefore included mediastinum imaging, hence the frequent finding of rebound mediastinal mass, as compared with an initial tumor site other than the mediastinum which may not have the same care for mediastinum imaging schedule after the end of treatment.

Most of our study population who presented a rebound thymic hyperplasia at follow-up did not experience a change in

the management of their follow-up after the discovery of this imaging finding. This shows that most clinicians are already aware of this phenomenon and tend to be reassured by the radiologic description of the rebound mass when it is described as benign. However, there are still 12 patients who had additional imaging, even though the description of their rebound mass suggested a diagnosis of rebound thymic hyperplasia, thus adding unnecessary diagnostic procedures and anxiety for the patients and their families. Better knowledge of rebound thymic hyperplasia could help establish a standard for the management of rebound mediastinal masse at follow-up.

Most rebound thymic hyperplasia was described on imaging as being a mediastinal mass of a triangular shape, with well-defined margins and a mild and homogenous enhancement, which did not invade the vessels and remained unchanged or diminished at follow-up. For the few patients who did have a tumor relapse, all had other radiologic signs of relapse, including multiple lymphadenopathies, which suggested a more concerning diagnostic than rebound thymic hyperplasia. These findings are consistent with previous studies describing the CT-scan imaging studies of adult patients with thymic enlargement following chemotherapy, with the rebound thymus described as being a triangular structure with homogenous enhancement, in the anterior mediastinum[24].

Unfortunately, given our limited number of patients, we were unable to find a clinical or demographic characteristic that clearly predicted the apparition of a rebound thymic hyperplasia. However, it seemed that age at diagnosis <14 years old was a risk factor for developing thymic hyperplasia. This is consistent with the fact the thymus is an organ that undergoes atrophy and involution with adulthood, and is more prominent in younger children[22]. This finding is also consistent with a previous study from Hu et al which described risk factors for reactive thymic hyperplasia in children with lymphoma following chemotherapy[26]. They found a higher prevalence of rebound thymic hyperplasia within the 2-12-year-old group compared to the 13-18-year-old group. They also found that the absence of mediastinal radiation therapy was predictor of thymic hyperplasia but this was not a significant risk factor in our patient population. Also, they described a proportion of 57% of patients having initial thymic infiltration at baseline who developed a thymic hyperplasia during follow-up after the end of chemotherapy. Even if we did not review the initial imaging at diagnostic in our study, we selected a cohort of patients with primary mediastinal lymphoma including probably thymic infiltration for most of them and the incidence of benign thymic enlargement is similar to their study result.

The main strength of our study was the retrospective review of all patients being treated for a mediastinal lymphoma, and not only patients with a known mediastinal rebound mass with no consideration to their primary lymphoma or histological type. The study was able to determine the incidence of this phenomenon, the main

goal being to avoid unnecessary additional imaging and invasive procedures. The collaboration with a radiology specialist allowed us to review available CT-scan images to help describe rebound masses and their evolution in time.

Unfortunately, given our study period that went back as far as 1994, the patients had a heterogeneous follow-up, as the standard of care in oncology changed greatly during this period. The diagnostic imaging was also different at the beginning of the study, which means that the amount of mediastinal rebound masses may have been underestimated by the old imaging technology. Furthermore, because of a rearrangement of the archives at our main study center, some medical records were available on computer while others were only in paper version, which may have influenced our data collection. In addition, old imaging studies were not available anymore for reviewing, and we were only able to rely on the initial imaging report by the radiologist at the time. However, we managed to minimize that heterogeneity by asking a radiology specialist to review most of the imaging studies of the patients who had a mass at follow-up. Lastly, we studied only patients with mediastinal lymphoma at diagnosis. However, as all lymphomas can have a relapse distant from the site of the initial tumor and rebound thymic hyperplasia following chemotherapy, it could be interesting to include those patients in further investigations.

2.5 CONCLUSION

Rebound thymic hyperplasia is a common phenomenon following chemotherapy for mediastinal lymphoma, nearly half of our study population having developed it during the first two years after the end of treatment. Some radiologic characteristics may orientate the diagnosis to rebound thymic hyperplasia, namely as triangular shape, well-defined margins, mild homogenous enhancement as well as absence of multiples lymphadenopathies. Additional imaging study should be limited to patients whose characteristics of the rebound mass or symptoms make the clinician suspect a tumor relapse. A prospective cohort study with standardized care should be conducted to better characterize rebound thymic hyperplasia and help clinicians in their approach to rebound mediastinal masses at follow-up.

2.6 CONFLICT OF INTEREST

The authors have no conflicts of interest or funding sources to disclose.

2.7 ACKNOWLEDGMENTS

We thank Dr Geneviève Morissette MD FRCPC for her guidance and support and Ms Stephanie Viel for manuscript language review from the CHU de Québec-Université Laval.

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3. Additional Material

TABLE S1 - Description of Patients with Mediastinal Tumor Relapse								
Patient	**Sex**	**Age at diagnosis (years)**	**Lymphoma**	**Type**	**Stage**	**Discovery of mediastinal mass (months post treatment)**	**Radiologic Description**	**Clinical Findings**
1	M	15.4	H	NS	II	12.7	Multiple mediastinal lymphadenopathies, diffuse heterogeneous mass with high enhancement	No B symptoms, clinical lymphadenopathy
2	M	8.4	NH	Ana	IV	2.3	Multiple mediastinal lymphadenopathies, homogeneous trapezoid mass	B symptoms present
3	F	15.1	H	NS	II	1.6	Diffuse mediastinal mass, heterogeneous moderate enhancement, ill-defined margins. Suspicious paratracheal lymphadenopathy	No symptoms
H: Hodgkin, NH: Non-Hodgkin, NS: nodular sclerosis, Ana: anaplastic								

Supplementary Table S1: Description of patients with mediastinal tumor relapse