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Rare Primary Thymic T-Lymphoblastic Lymphoma In Childhood- Clinical Case From Our Practice

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1. Abstract

As stated in the current World Health Organization classification, T-lymphoblastic leukemia/lymphoma is a neoplasm of lymphoblasts committed to T-cell lineage involving bone marrow (BM), blood, or presenting as a tissue-based mass involving the thymus, lymph nodes, or extranodal sites. We present a 10 -year -old boy who is a family -burdened mucoviscidosis. Imaging studies report an extended anterior mediastinum. After the first biopsy, the final diagnosis is difficult, which significantly slows down the necessary treatment. Prolonged treatment with corticosteroids and a heterozygous family-burdened mucoviscidosis is the cause of severe chemotoxicity after one course of chemotherapy. This is the reason for the completion of treatment by consolidating involved site radiotherapy.

The primary thymic Non-Hodgkin lymphoma is a rare disease. Diagnosis is extremely difficult and requires a biopsy of the tumor and bone marrow, strictly pathohistological and immunohistochemical analysis, as well as imaging studies involving CT and PET/CT. The clinical case focuses on the difficult final diagnosis, as well as the need for consolidating involved site radiotherapy of mediastinal tumor mass with a radical dose with strictly preserving the adjacent normal tissues and organs.

2. Introduction

Thymic neoplasms are a heterogeneous group of tumors and are the most common neoplasms of the anterior mediastinum [1]. T-acute lymphoblastic leukemia (T-ALL) and T- lymphoblastic lymphoma (T-LBL) are neoplasms of immature T-cell precursors or lymphoblasts [2]. As stated in the current World Health Organization classification, T-lymphoblastic leukemia/lymphoma is a neoplasm of lymphoblasts committed to T-cell lineage involving bone marrow (BM), blood, or presenting as a tissue-based mass involving the thymus, lymph nodes, or extranodal sites [3].T-ALL represents around 25% of all adult cases of ALL. In contrast with T-ALL, T-LBL is far more common than B-lymphoblastic lymphoma; 85% to 90% of all cases of T-LBL are of T-cell lineage [4]. The most common anterior mediastinal NHLs (90% to 95%) are primary mediastinal (PM) large B-cell lymphoma and T-lymphoblastic lymphoma[5]. Patients with T-ALL/T-LBL have clinically aggressive disease[6]. We present an extremely rare clinical case for a child with mediastinal tumor in the anterior mediastinum who was diagnosed as thymic T- lymphlastic lymphoma (T-LBL).

3. Clinical Case

We present a 10 -year -old boy who is a family -burdened mucoviscidosis/ father with proven mucoviscidosis. In January 2022, complaints of fever and cough began. After one month, shortness of breath, cyanosis and cough suddenly occur from the antibiotic treatment. As this condition is evaluated as an allergic manifestation, after treatment with urbazone the child improves. After 10 days, the child had shortness of breath, rapid breathing, edema of the face and cyanosis. After a lung radiography, an extended upper mediastinum was found (Figure 1). The CT of the upper anterior

mediastinum found a tumor mass. Consultation with a hematologist was consulted and a corticosteroid treatment for the vena cava syndrome began. After improving the condition and a significant reduction in mediastinal formation, a biopsy through video assisted thoracic surgery (VATS) was performed. (VATS). Due to the presence of infiltration from inflammatory cells, single calcifications, focal necrosis, units of small monomorphic cells with oval nucleus, without giant cells, the histological result was judged as a lymphoproliferative process or thymom, including a sclerosing histological features. The child was admitted to the Clinic of Pediatric Clinical Hematology and Oncology in March 2022 in a satisfactory general condition without fever. Paraclinical studies have detected leukocytosis (WBC-34,98 g/l), biochemical tests were within normal limits, bone marrow without pathological infiltration, and the bone marrow immunoflourcitometry (IF) does not report clonal data in the material presented. Polymerase Chain Reaction (PCR) does not establish the most common molecular equivalents characteristic of acute lymphoblastic leukemia in childhood. From the thorax CT / Март 2022 - There is no data on significant cervical adenomegaly. Retrosternally visualizes a 53 x 24 mm soft tissue formation with a light -grade compression of the vena brahiocephalica. No nodular lesions/ lymphoid infiltrates are found in the pulmonary parenchyma. There are no pericardial and pleural effusion. Bone structures are normal (Figure 2). March 2022 was conducted 18F-FDG PET/CT, which retrosterly reported discrete immeasurable changes with the background accumulation of marked glucose, and from the CT the presence of a vaguely demarned soft tissue finding, difficult to distinguish from the adjacent lymph nodes located in the neighborhood (Figure 3). The revision of histological results found that at its first processing the material was technically compromised, which impedes the overall judgment. Fatty and predominantly fibrous tissue with hyalinosis, a significant number of vessels and infiltration of mature lymphoid cells are reported. Immunohistochemistry reports positive CD3 and CD20 expression in part of the lymphoid cells; positive CD15 expression in the granulocytes, mainly in the lumen of the vessels; negative CD30 expression after double marking; positive PAX-5 nuclear expression in the B-lymphocytes. Conclusion- The material does not allow the nosological category to define, which requires examination of a reserve or new biopsy material. Due to the lack of clearly established histological verification of the pathological process, corticosteroid therapy was gradually reduced and discontinued. The child was evaluated for active monitoring and planning a new biopsy with subsequent histological examination. In May 2022, the thorax CT found an increased volume of retrosternal mass (Figure 4), on which a repeated VATS biopsy was performed. The histological result was a lymphoproliferative process made up of monomorphic lymphoid cells with diffuse growth without morphologically distinct epithelial structures. The immunohistochemical examination reports CD3-positive reaction, KI 67 positive reaction above 90%, CD15 and CD20-negative reaction. The find corresponds to a Non-Hodgkin T-cell lymphoma. Bone-marrow biopsy reports hyperplastic bone marrow without parablastic infiltration, and the immunoflourcitometry of the bone marrow does not identify T- T-lymfoblasts. PCR does not detect SIL-TAL1 fusion gene transcripts and overexpression of the HOX11 gene. The lumbar puncture reports a normal cerebrospinal liquor. After discussing the necessary induction treatment under the ALL IC-BFM2009 protocol was started. Induction treatment under the ALL IC-BFM2009 protocol was started. In the treatment course, a gradually developing muscle weakness occurs, probably as a result of drug -induced polyneuropathy and myopathy. At the end of the induction phase, against the background of progressively induced bone marrow aplasia, a progressively increased volumetric hepatomegaly develops up to 5-6 cm below the rib arc with a appearance of a subicter on the skin and sclera. Paraclinic studies have evidence of hyperbilirubinemia, progressing cytolithic syndrome, hyperamoniamia, moderately elevated values of pancreatic enzymes, hypoproteinemia with pronounced hypoalbuminemia. The child was translated into an intensive sector with sepsis, subileus, severely induced bone marrow hypoplasia, severe toxic hepatitis and dyselectrolytemia. After intensive and complex treatment for one month, the child's difficult condition was mastered. This was followed by a patient's clinical monitoring period and conducting control studies without taking new therapy due to the observed severe side complications of the treatment. Thorax CT from 27.09.22- The tracked formation behind the sterum, covering the thymus and the anterior upper mediastinum changes its size from 53x24 mm to 30x15 mm, and currently the thymus gland is visible in the area of interest. No vascular compression data and no focal and infiltrative changes in the bilateral lung parenchyma. No data on pleural and pericardial effusion. Conclusion- Reduction of the dimensions of the retrosternal formation (Figure 5). CT of abdomen from 27.09.22- without pathological changes in the abdominal organs. Liver with normal shape and enlarged size. Inhomogeneous hypogenic structure without data on focal lesions. Paraclinic studies are normal without leukocytosis, biochemistry is normal. In the December 2022 chest CT reported an increase in the retrosternal mass in the anterior upper mediastinum, which has lobulated contours and homogeneous density. No vascular compression data and no focal and infiltrative changes in the bilateral lung parenchyma. No data on pleural and pericardial effusion. (Figure 6). 18F-FDG PET/ CT from January 2023-Persistence of the retrosteneal formation in the front mediastinum, which now presents more formulated, with lobulated contours and a homogeneous metabolic activity SUV max 3.3 (Figure 7). The case was discussed by the Onco -Hematological Committee on the current clinical condition, the adverse dynamics after the induction treatment of the underlying disease and the subsequent therapeutic strategy in the child. The unusual toxicity of induction treatment was most likely due to prolonged treatment with corticosteroids prior to determining the

final diagnosis, as well as to heterozygous familial burden of cystic fibrosis disease. We estimated that a discontinuation of chemotherapy was required, but a consolidating radiotherapy (RT) of the retrosternal mass was required. The child was aimed at conducting intensity modulated radiotherapy (IMRT) of the tumor localized in the front upper mediastinum. In RT preparation, we have prepared two anatomy- topographical and dosimetric plans for the consolidating involved site radiotherapy by the VMAT method. The first plan is a free-breathing radiotherapy (Figure 8) and the second in deep inspiration breath-hold RT technique (Figure 9). After comparing the dosimetric distribution of radiation doses in the critical organs / heart and in the lungs without the planned tumor volume (PTV), a significant reduction in these doses was detected in the deep inspiration breath hold RT technique (Figure 10 and 11). After fusion of the PET/ CT and planning CT images, we determined the clinical target volume (CTV). With the deep inspiration breath-hold RT technique, in the planned targeted volume (PTV) including the retrosternal tumor, we have realized a total dose (TD) 25.2 Gy with a daily dose (DD) 1.8 Gy. The child suffered the consolidating involved site radiotherapy very well, without early radiation toxicity. After 2 months of the completion of RT, the child was directed for restoring PET/CT.

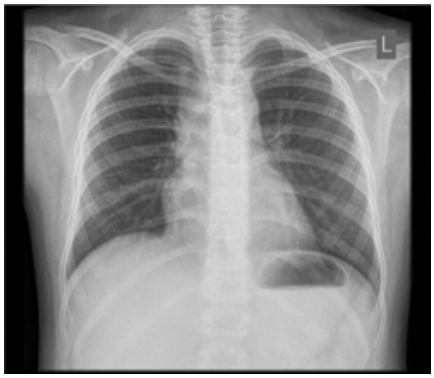

Figure 1: Pulmonary radiography from March 2022.

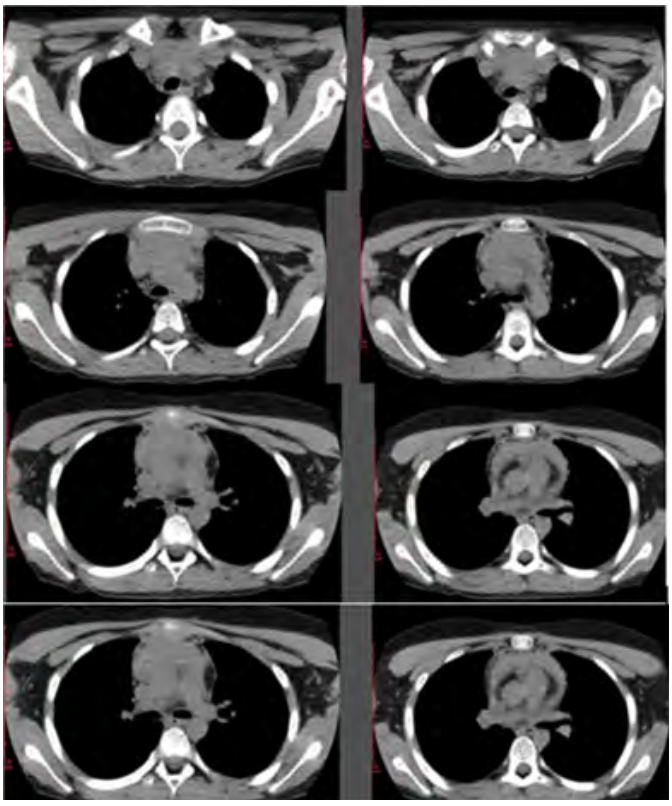

Figure 2: CT of thorax from March 2022.

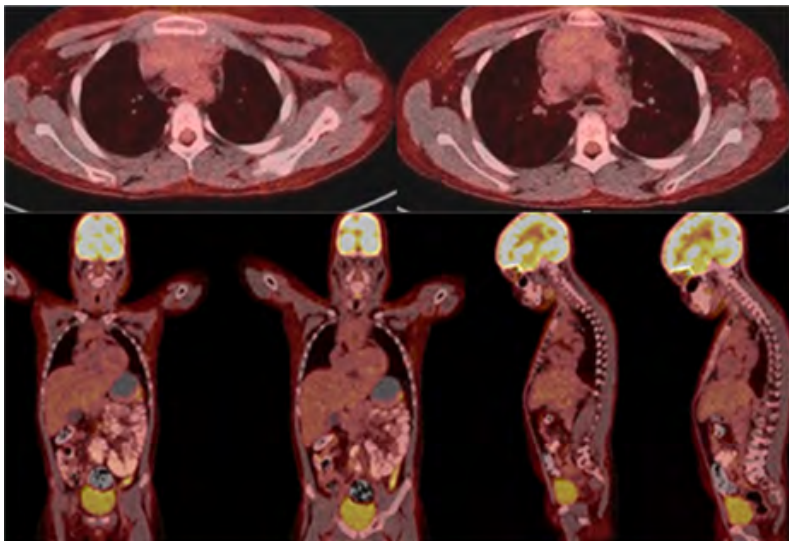

Figure 3: 18F-FDG PET/CT from March 2022, there are no metabolically active areas throughout the body

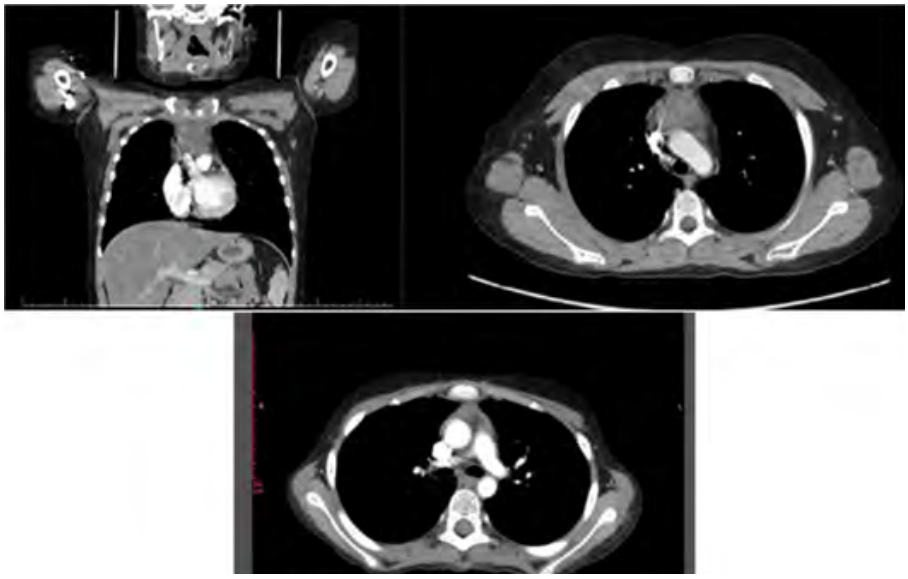

Figure 4: CT of thorax from May 2022.

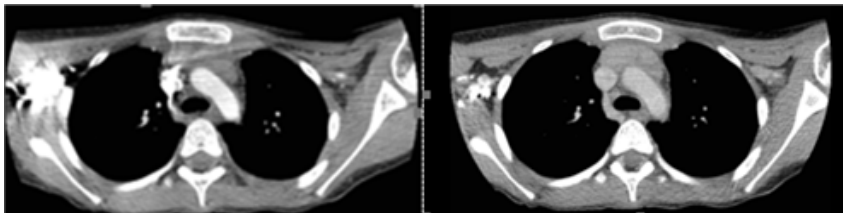

Figure 5: CT of thorax from September 2022.

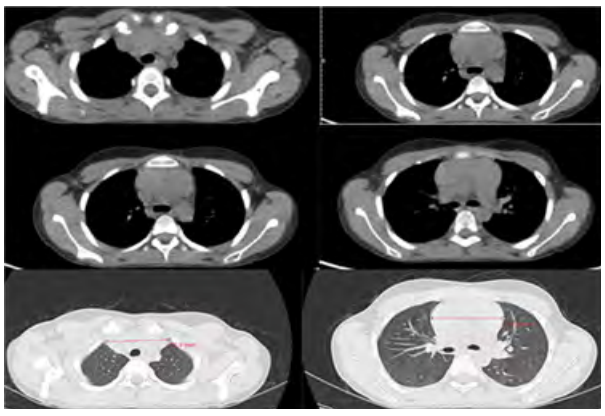

Figure 6: CT of thorax from December 2022- The last two slides show the image of a lung window.

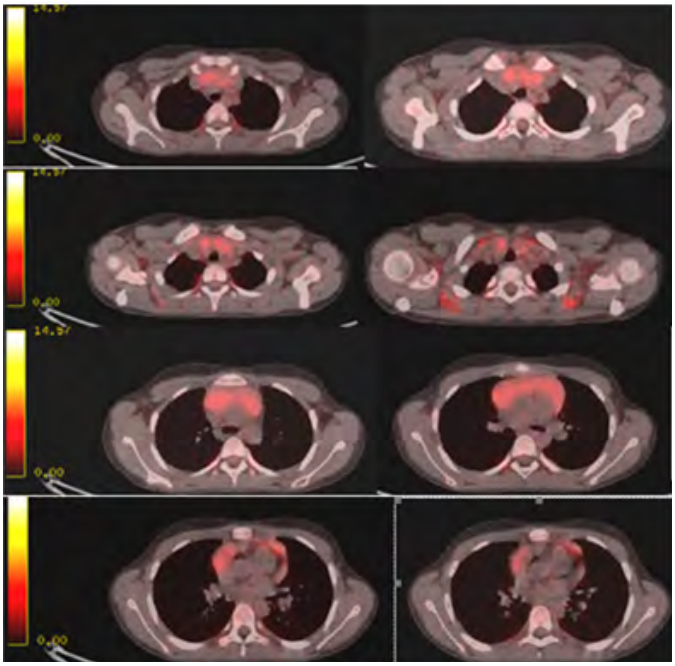

Figure 7: 18F-FDG PET/ CT from January 2023-Persistence of the retrosteneal formation in the front mediastinum, which now presents more formulated, with lobulated contours and a homogeneous metabolic activity SUV max 3.3 .

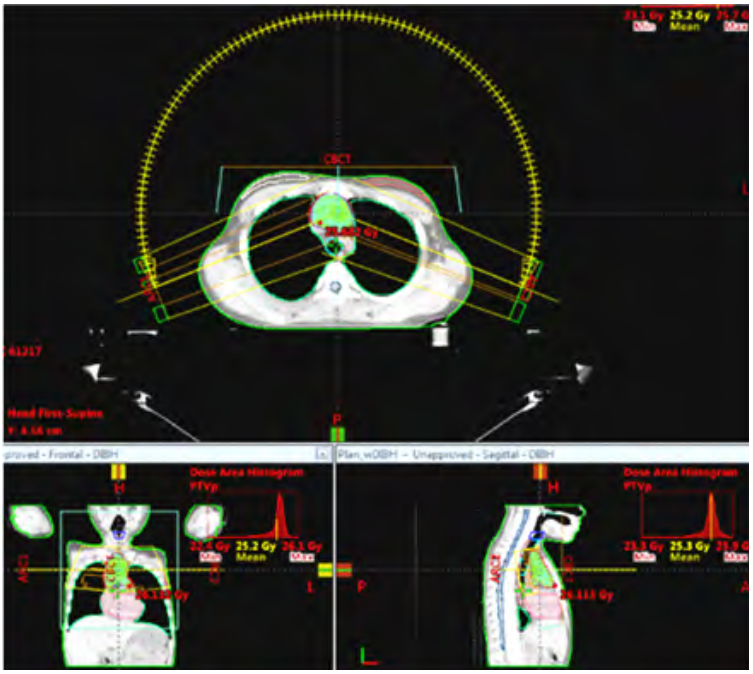

Figure 8: Free-breathing radiotherapy by the VMAT method.

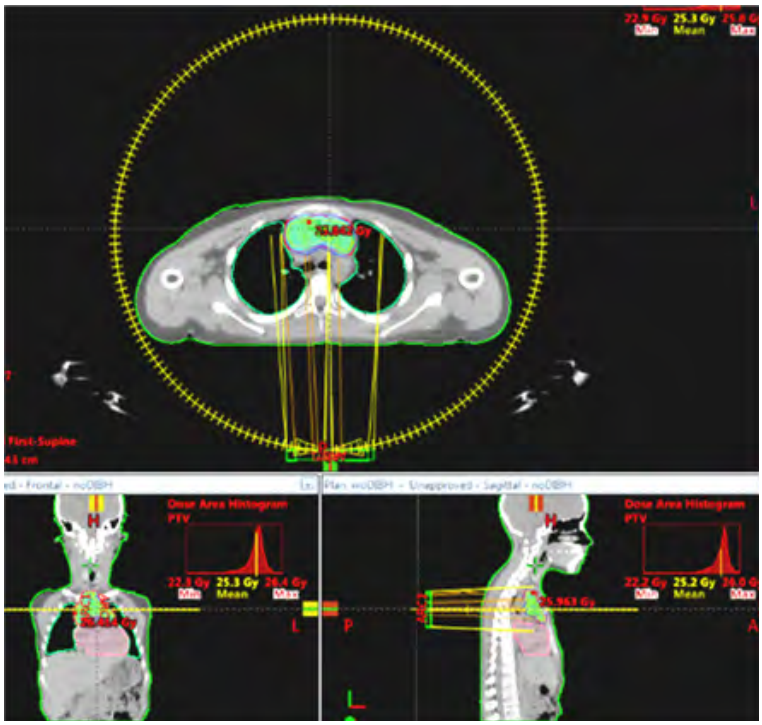

Figure 9: Deep inspiration breath-hold RT technique by the VMAT method.

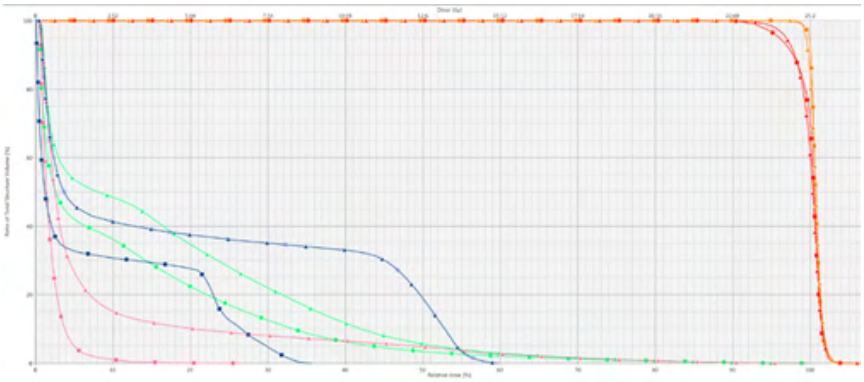

Figure 10: A comparative analysis of the distribution of radiation doses in target volumes/ CTV and PTV/ and in the critical organs/ heart, lungs and larynx/ in both RT methods with free and retained breathing. Free breathing curves are marked with a triangle and the curves in the hold of the breathing with a square.The red curves show target volumes, the blue larynx, the green- the lungs without the pulmonary PTV, and the pink- the heart.

Show DVH	Structure	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
▲	myelon	22.3	100.0	99.7	0.025	8.995	2.104
■	larynx	19.5	100.0	100.1	0.157	0.936	0.325
▲	larynx						
■	humeros sin	29.2	100.0	100.0	0.196	1.270	0.502
■	humeros dex	37.1	100.0	100.0	0.167	2.099	0.818
■	esophagus	2.2	100.0	100.2	0.553	23.652	8.770
▲	esophagus						
■	cor	313.9	100.0	100.0	0.134	25.178	2.013
▲	cor	234.9	100.0	100.0	0.092	6.694	0.499
■	body	14968.0	100.0	100.1	0.000	26.958	1.499
▲	body	12268.5	100.0	100.0	0.000	26.777	1.827
■	Trachea	3.7	100.0	100.0	0.539	2.618	1.075
▲	Trachea						
■	Thyroid	2.5	100.0	100.0	0.355	0.744	0.526
▲	Thyroid						
■	RightArm	905.9	100.0	100.0	0.000	2.726	0.608
■	RBNG	833.3	100.0	100.0	0.249	24.703	8.195
▲	RBNG						
▲	PTVp	112.0	100.0	100.1	21.618	26.593	25.200
■	PTV	118.3	100.0	99.9	21.718	26.958	25.200
■	Lung_R	677.9	100.0	100.0	0.162	24.471	3.954
■	Lung_L	489.9	100.0	100.1	0.100	25.891	4.472

Figure 11: Table representing the radiation doses in the critical organs / max, min and mean / in both dosimetrically planned methodologies. In the free breathing RT method, they are marked with a triangle and in the hold of the breathing RT with a square.

4. Discussion

The mediastinum is the common site for the occurrence of malignant lymphoma [7]. Lymphoma is one of the most common malignancies which can occur in different organs and tissues throughout the body, which includes Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) [8]. Primary mediastinal non-Hodgkin's lymphomas (PM-NHLs) represent ∼5% of all non-Hodgkin lymphomas (NHLs) and comprise lymphomas of B-cell and T-cell origin [9] They are an extremely rare kind of tumor, and they are lack of large-scale studies or definite guidelines to describe its clinical characteristics, treatment, and prognosis [10,11].The thymus, located in the anterior mediastinum, is the primary anatomic site of T cell development. Therefore, it is not surprising that many lymphoid malignant neoplasms arising within the thymus are T cell neoplasms, mostly T cell lymphoblastic lymphoma (T-LBL) [5]. T-LBL is the most common lymphoma of children and most arise in the thymus [12]. Based on previous studies, there were only case reports or cases series of small sample size for thymic lymphoma [13-16]. According to the WHO classification of lymphoma, primary thymic large B-cell lymphoma (PTLBL) is the predominant pathological type of thymic lymphoma [17]. The initial clinical manifestation in T-LBL, which accounts for approximately one quarter of childhood non-Hodgkin lymphoma, usually takes the form of a mediastinal mass or lymphadenopathy whereas T-ALL patients present with predominantly bone marrow and peripheral blood disease manifestations [18]. PM-NHLs are defined as involvement of mediastinal lymph nodes, thymus, and/or mediastinal organs (heart, lung, pleura, pericardium) by NHL without evidence of systemic disease at presentation [5]. Patients with <25% bone marrow involvement are classified as T-LBL while patients with 25% or more bone marrow blasts are diagnosed with T-ALL [19]. Both thymoma and T lymphoblastic leukemia/lymphoma arise in mediastinum, and the immature lymphocytes associated with thymoma may resemble T lymphoblastic leukemia/lymphoma cells [20]. Lymphoma occurring in patients with a prior history of a thymoma has also been described in the literature, albeit rarely [21-24]. CT scan is very useful for assessing the invasion of adjacent structures, although MRI has been used in recent years since the images can better distinguish the thymic tumor from neighboring structures [25]. In the clinical case presented from the chest CT visualizes a retrosternal soft tissue formation 53 x 24 mm with a light -grade compression of the vena brahiocephalica. No nodular lesions/ lymphoid infiltrates are found in the pulmonary parenchyma (Figure 2). Positron emission tomography (PET) and gammagraphy with gallium 67 currently seem to be the most useful for determining whether residual area harbors tumor activity or merely fibrosis [7]. In the clinical case presented, 18F-FDG PET/ CT from March 2022 does not take into account increased metabolic activity in the retrosternal tumor (Figure 3). Delayed diagnosis and inadequate initial therapy may comprise the potential for salvage and long-term survival [26]. Distinguishing between thymoma and T-lymphoblastic lymphoma/leukemia may be challenging and requires multimodality diagnostic approaches using histological, immunophenotyping, and molecular testing [27]. In Non- Hodgkin's lymphoma cellularity may be quite limited when sclerotic [12]. The distinction between thymoma and T lymphoblastic leukemia/lymphoma is occasionally difficult, because the immature lymphocytes associated with thymoma may resemble T lymphoblastic leukemia/lymphoma cells, both morphologically and immunohistochemically [20]. Pathological analysis of T-lymphoblastic leukemia/ lymphoma, showing sheets of T-cell lymphoblasts positive for CD3, CD5, CD1a, and TdT and complete absence of epithelial cells with negative keratin markers [27,28]. The histological result in our patient after the first biopsy is judged as a lymphoproliferative process or thymoma, including a sclerosing histological features, due to the presence of infiltration from inflammatory cells, single calcifications, focal necrosis, units of small monomorphic cells with oval nucleus, without giant cells. Macroscopically, the thymus involved by Hodgkin's lymphoma show multiple firm white nodules with or without visible fibrous bands. On histological study, the most common type is nodular sclerosis, as the other types typically affect lymph nodes except the thymus[29]. in our patient a second biopsy was required via VATS, which is a minimally invasive surgical approach. The histological result is judged as a lymphoproliferative process made up of monomorphic lymphoid cells with diffuse growth without morphologically distinct epithelial structures. A immunohistochemical examination reports CD3-positive reaction, KI 67 positive reaction above 90%, CD15 and CD20-negative reaction. Flow cytometry (FC) is helpful for the classification of non-Hodgkin lymphoma [12]. FC remains an important tool in distinguishing benign thymocytes from T-lymphoblastic lymphoma/leukemia lymphoblasts based on their distinct patterns of antigen expression [30,31]. The bone-marrow biopsy in our patient reports hyperplastic bone marrow without parablastic infiltration, and the bone marrow immunoflow cytometry (IFC) does not identify T-lymfoblasts. Another diagnostic tool is the assessment of characteristic cytogenetic or molecular abnormalities known to be associated with T-lymphoblastic lymphoma/leukemia, such as a monoclonal pattern of TCR-β and TCR-γ rearrangements by RT-PCR or the characteristic translocations or NOTCH1/FBXW7 mutations which are frequently found in neoplastic T lymphoblasts as opposed to normal thymocytes [32]. In our patient PCR does not detect SIL-TAL1 fusion gene transcripts and overexpression of the HOX11 gene. The lumbar puncture reports a normal cerebrospinal liquor. Thus, the final diagnosis was made thymic Non- Hodgkin's T-lymphoblastic lymphoma.

In a patient with thymic tumour with a preoperative or intraoperative study suspected of having a lymphoma, it is necessary to do a biopsy and not resective surgery, to avoid unnecessary resec-

tions and morbidity. The main treatment is radiotherapy (RT) and chemotherapy (Ch), with associated bone marrow transplantation in selected cases [33]. Due to severe toxicity after one Ch course, our patient was targeted for intensity modulated radiotherapy (IMRT) in the area of anterior upper mediastinal retrosternal tumor. We conducted deep inspiration breath-hold RT by the VMAT method, which reduces the radiation dose in the critical organs near the target volume, mainly in the lungs and heart (Figure 9 and 11). This RT methodology is required for the RT of malignant mediastinal processes. In the target volumes (CTV and PTV) including the mediastinal tumor, we realized up to TD 25,2 Gy with DD1.8 Gy (Figure 9). The child suffered the radiation treatment very well, without early radiation toxicity. After 2 months of the completion of RT, the child is directed for restoring PET/CT.

5. Conclusion

The primary thymic Non-Hodgkin's lymphoma is a rare malignancy, both in mature and childhood. Diagnosis is extremely difficult and requires a biopsy of the tumor and bone marrow, strictly pathohistological and immunohistochemical examination, as well as imaging studies involving CT and PET/CT. The clinical case presented focuses on the difficult final diagnosis, which slows down the initiation of the necessary treatment and thus worsens the prognosis. Prolonged treatment with corticosteroids and a heterozygous family -burdened mucoviscidosis is the cause of severe chemotoxicity after one course of chemotherapy. This is the reason for the completion of treatment by consolidating involved site radiotherapy. We conducted deep inspiration breath-hold RT technique by the VMAT method, which reduces the radiation dose in the critical organs near the target volumes, mainly in the lungs and heart. This RT methodology is required in the irradiation treatment of malignant mediastinal processes.

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