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# RarePrimaryThymicT-LymphoblasticLymphomaInChildhood-ClinicalCaseFromOur Practice

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## 1. Abstract

AsstatedinthecurrentWorldHealthOrganizationclassification, 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 whoisafamily-burdenedmucoviscidosis.Imagingstudiesreport 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 CTand PET/CT.Theclinicalcasefocusesonthedifficultfinaldiagnosis, aswellastheneedforconsolidatinginvolvedsiteradiotherapyof mediastinaltumormasswitharadicaldosewithstrictlypreserving the adjacent normal tissues and organs.

## 2. Introduction

Thymic neoplasms are a heterogeneous group of tumors and are themostcommonneoplasmsoftheanteriormediastinum[1].

T-acute lymphoblastic leukemia (T-ALL) and T- lymphoblastic lymphoma (T-LBL) are neoplasms of immatureT-cell precursors orlymphoblasts[2].AsstatedinthecurrentWorldHealthOrganization 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 involvingthethymus,lymphnodes,orextranodalsites[3].T-ALL represents around 25% of all adult cases ofALL. In contrast with T-ALL, T-LBL is far more common than B-lymphoblastic lymphoma;85%to90%ofallcasesofT-LBLareofT-celllineage[4]. The most common anterior mediastinal NHLs (90% to 95%) are primary mediastinal (PM) large B-cell lymphoma and T-lymphoblasticlymphoma[5].PatientswithT-ALL/T-LBLhaveclinically aggressive disease[6]. We present an extremely rare clinical case for a child with mediastinal tumor in the anteriormediastinum whowasdiagnosedasthymicT-lymphlasticlymphoma(T-LBL).

## 3. Clinical Case

Wepresenta10-year-oldboywhoisafamily-burdenedmucoviscidosis/ 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 thefaceandcyanosis.Afteralungradiography,anextendedupper mediastinumwasfound(Figure1).TheCToftheupperanterior

mediastinum found a tumor mass. Consultation with a hematologistwasconsultedandacorticosteroidtreatmentforthevenacava syndrome began.After improving the condition and a significant reductioninmediastinalformation,abiopsythroughvideoassist- ed 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,withoutgiantcells,thehistologicalresultwasjudgedasa lymphoproliferative process or thymom, including a sclerosing histologicalfeatures.ThechildwasadmittedtotheClinicofPediatricClinicalHematologyandOncologyinMarch2022inasatisfactory 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 marrowimmunoflourcitometry (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.FromthethoraxCT/Mapr2022-Thereisnodataon significantcervicaladenomegaly.Retrosternallyvisualizesa53x 24mmsofttissueformationwithalight-gradecompressionofthe venabrahiocephalica.Nonodularlesions/lymphoidinfiltratesare foundinthepulmonaryparenchyma.Therearenopericardialand pleural effusion. Bone structures are normal (Figure 2). March 2022wasconducted18F-FDGPET/CT,whichretrosterlyreported discreteimmeasurablechangeswiththebackgroundaccumulation of marked glucose, and from the CT the presence of a vaguely demarnedsofttissuefinding,difficulttodistinguishfromtheadja- cent lymph nodes located in the neighborhood (Figure 3).The revision of histological results found that at its first processing the materialwastechnicallycompromised,whichimpedestheoverall judgment.Fattyandpredominantlyfibroustissuewithhyalinosis, asignificantnumberofvesselsandinfiltrationofmaturelymphoid cells are reported. Immunohistochemistry reports positiveCD3 andCD20expressioninpartofthelymphoidcells;positiveCD15 expressioninthegranulocytes,mainlyinthelumenofthevessels; negative CD30 expression after double marking; positive PAX-5 nuclearexpressionintheB-lymphocytes.Conclusion-Thematerialdoesnotallowthenosologicalcategorytodefine,whichrequires examination of a reserve or new biopsy material. Due to the lack of clearly established histological verification of the pathological process,corticosteroidtherapywasgraduallyreducedanddiscontinued. The child was evaluated for active monitoring and planning a new biopsy with subsequent histological examination. In May 2022, the thorax CTfound an increased volume of retrosternal mass (Figure 4), on which a repeated VATS biopsy was performed.Thehistologicalresultwasalymphoproliferativeprocess made up of monomorphic lymphoid cells with diffuse growth withoutmorphologicallydistinctepithelialstructures.Theimmunohistochemicalexaminationreports CD3-positivereaction,KI67 positive reaction above 90%, CD15 and CD20-negative reaction. ThefindcorrespondstoaNon-HodgkinT-celllymphoma. Bonemarrow biopsy reports hyperplastic bone marrow without parablasticinfiltration,andtheimmunoflourcitometryofthebone marrow does not identify T- T-lymfoblasts. PCR does not detect SIL-TAL1 fusion genetranscripts and overexpression of the HOX11gene.Thelumbarpunctureреportsanormalcerebrospinal liquor. After discussing the necessary induction treatment under the ALL IC-BFM2009 protocol was started. Induction treatment undertheALLIC-BFM2009protocolwasstarted.Inthetreatment course,agraduallydevelopingmuscleweaknessoccurs,probably asaresultofdrug-inducedpolyneuropathyandmyopathy.Atthe endoftheinductionphase,againstthebackgroundofprogressive- ly induced bone marrow aplasia, a progressively increased volumetrichepatomegalydevelopsupto5-6cmbelowtheribarcwith aappearanceofasubicterontheskinandsclera.Paraclinicstudies have evidence of hyperbilirubinemia, progressing cytolithic syndrome,hyperamoniamia,moderatelyelevatedvaluesofpancreatic enzymes, hypoproteinemia with pronounced hypoalbuminemia. The child was translated into an intensive sector with sepsis, subileus,severelyinducedbonemarrowhypoplasia,severetoxichepatitis 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 from27.09.22-Thetrackedformationbehindthesterum,covering the thymus and the anterior upper mediastinum changes its size from 53x24 mm to 30x15 mm, and currently the thymus gland is visibleintheareaofinterest.Novascularcompressiondataandno focalandinfiltrativechangesinthebilaterallungparenchyma.No dataonpleuralandpericardialeffusion.Conclusion-Reductionof the dimensions of the retrosternal formation (Figure 5). CTof abdomenfrom27.09.22-withoutpathologicalchangesintheabdominalorgans.Liverwithnormalshapeandenlargedsize.Inhomogeneoushypogenicstructurewithoutdataonfocallesions.Paraclinic studies are normal without leukocytosis, biochemistry is normal. IntheDecember2022chestCTreportedanincreaseintheretrosternalmassintheanterioruppermediastinum,whichhaslobulated contours and homogeneous density. No vascular compression data and no focal and infiltrative changes in the bilateral lung parenchyma.Nodataonpleuralandpericardialeffusion.(Figure6). 18F-FDGPET/CTfromJanuary2023-Persistenceoftheretrostenalformationinthefrontmediastinum,whichnowpresentsmore formulated,withlobulatedcontoursandahomogeneousmetabolic activity SUV max 3.3 (Figure 7). The case was discussed by the Onco-HematologicalCommitteeonthecurrentclinicalcondition, theadversedynamicsaftertheinductiontreatmentoftheunderly- ing disease and the subsequent therapeutic strategy in the child. Theunusualtoxicityofinductiontreatmentwasmostlikelydueto prolongedtreatmentwithcorticosteroidspriortodeterminingthe

finaldiagnosis,aswellastoheterozygousfamilialburdenofcystic-fibrosisdisease.Weestimatedthatadiscontinuationofchemotherapywasrequired,butaconsolidatingradiotherapy(RT)oftheretrosternalmasswasrequired.Thechildwasaimedatconducting intensitymodulatedradiotherapy(IMRT)ofthetumorlocalizedin thefrontuppermediastinum.InRTpreparation,wehaveprepared two anatomy- topographical and dosimetric plans for the consolidatinginvolvedsiteradiotherapybytheVMATmethod.Thefirst plan is a free-breathing radiotherapy (Figure 8) and the second in deep inspiration breath-hold RT technique (Figure 9).After comparingthedosimetricdistributionofradiationdosesinthecritical organs / heart and in the lungs without the planned tumor volume (PTV), a significant reduction in these doses was detected in the deepinspirationbreathholdRTtechnique(Figure10and11).AfterfusionofthePET/CTandplanningCTimages,wedetermined theclinicaltargetvolume(CTV).Withthedeepinspirationbreath-hold RTtechnique, in the planned targeted volume (PTV) includingtheretrosternaltumor,wehaverealizedatotaldose(TD)25.2 Gywithadailydose(DD)1.8Gy.Thechildsufferedtheconsolidatinginvolvedsiteradiotherapyverywell,withoutearlyradiation toxicity. After 2 months of the completion of RT, the child was directed for restoring PET/CT.

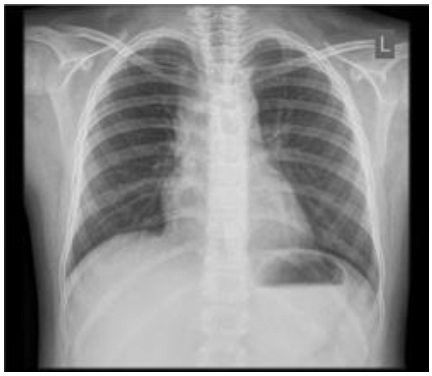

**Figure1:**Pulmonary radiographyfromMarch 2022.

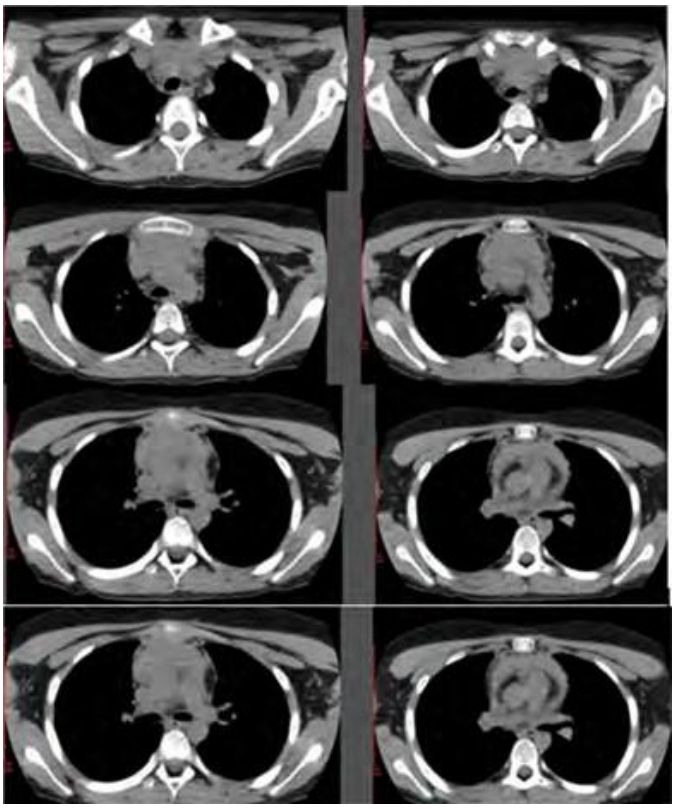

**Figure2:**CTofthorax fromMarch 2022.

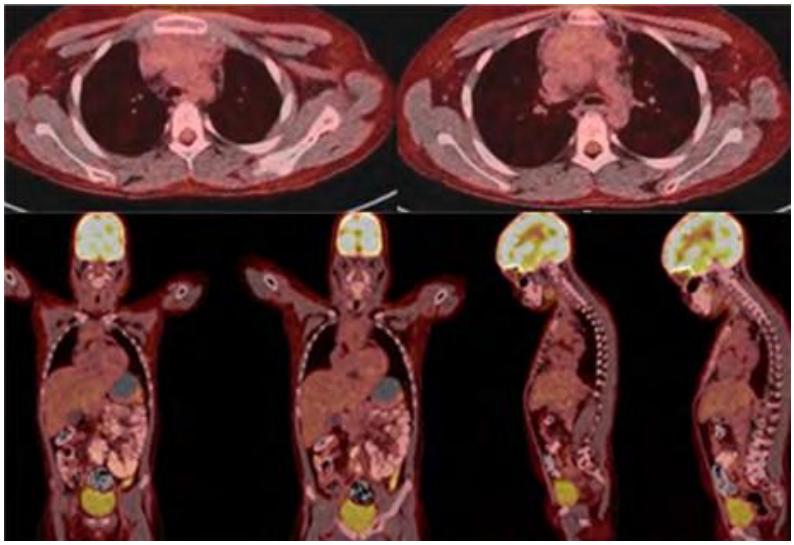

**Figure3:**18F-FDGPET/CTfromMarch2022,therearenometabolicallyactiveareasthroughoutthe body

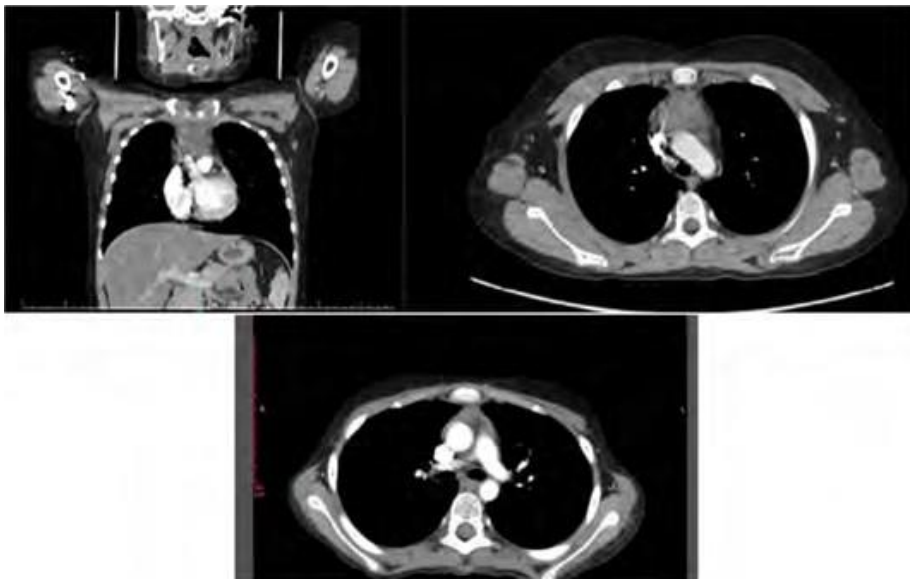

**Figure4:**CTofthorax fromMay 2022.

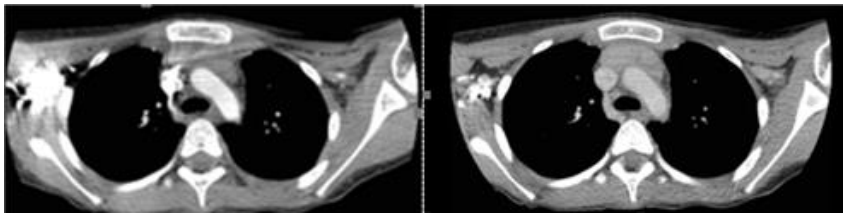

**Figure5:**CTofthorax fromSeptember 2022.

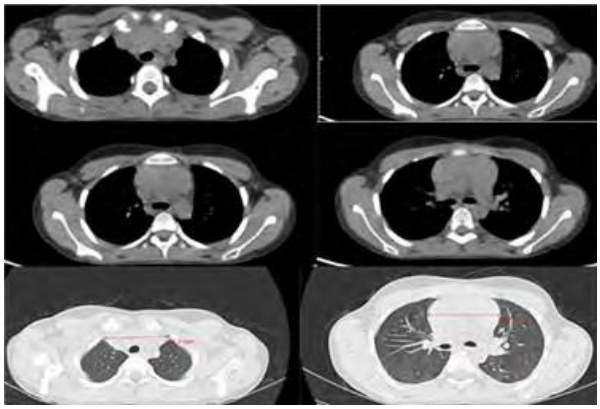

**Figure6:**CTofthoraxfrom December2022-The lasttwoslidesshowtheimage ofalung window.

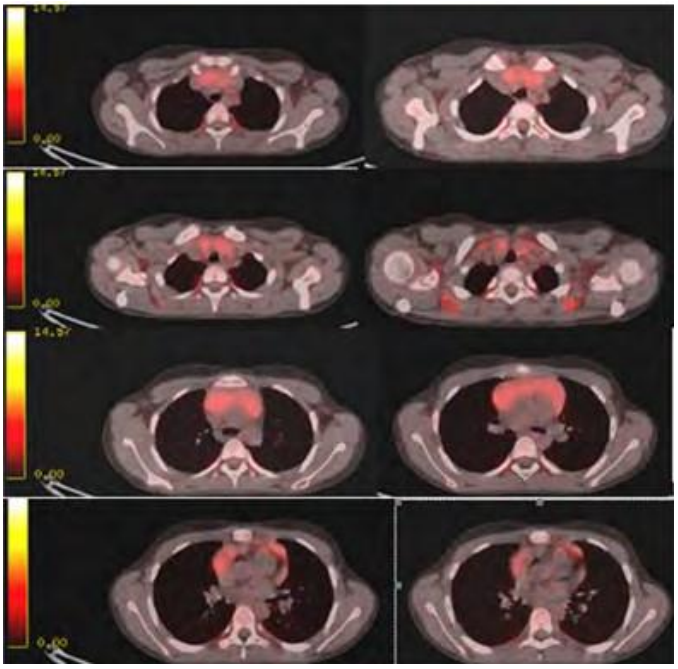

**Figure7:** 18F-FDGPET/CTfromJanuary2023-Persistenceoftheretrostenealformationinthefrontmediastinum,whichnowpresentsmoreformu- lated, with lobulated contours and a homogeneous metabolic activity SUV max 3.3 .

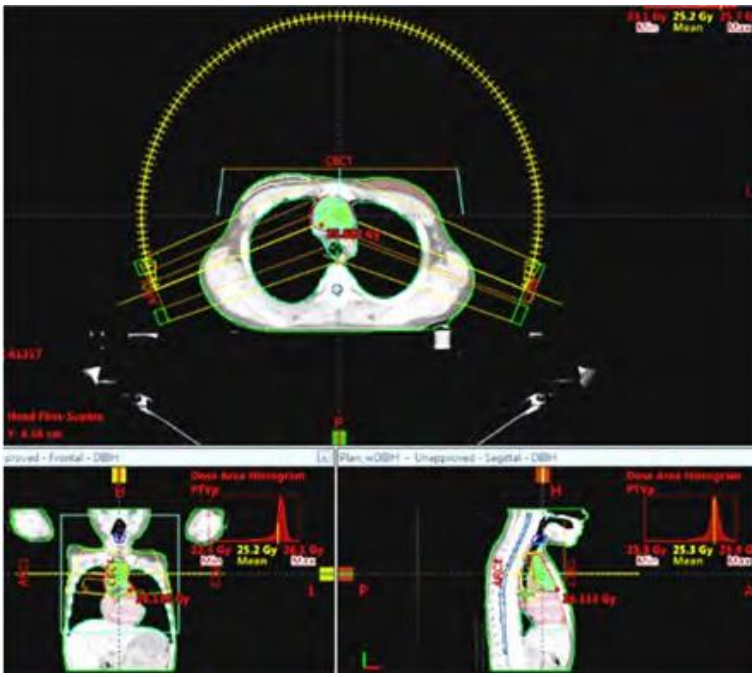

**Figure8:** Free-breathingradiotherapybytheVMATmethod.

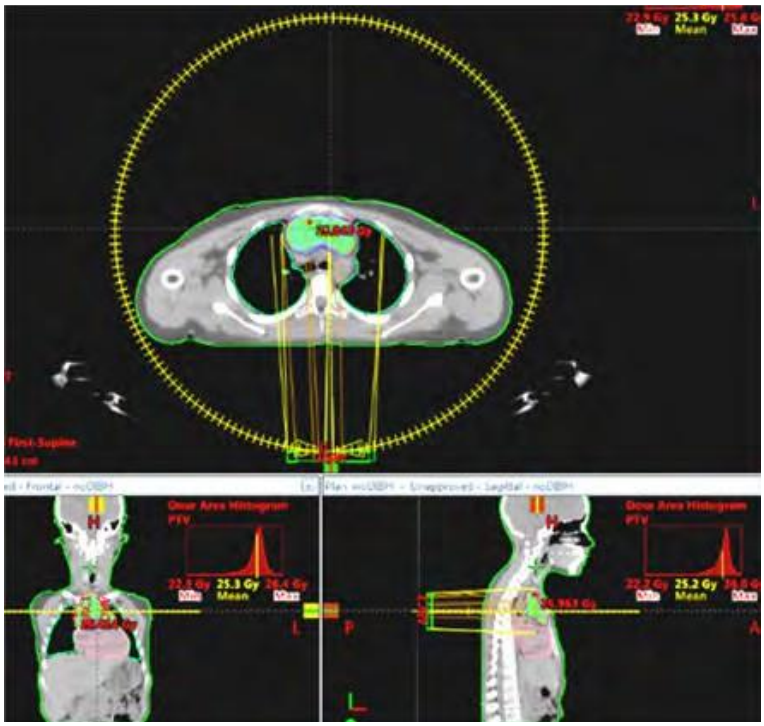


**Figure9:**DeepinspirationbreathRTtechniquebytheVMATmethod.

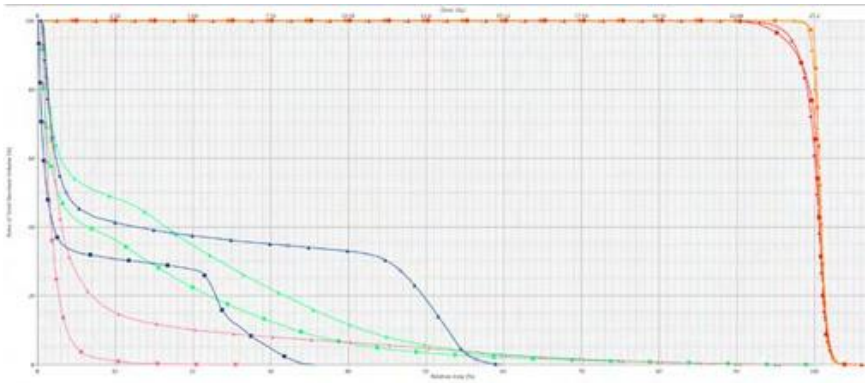

**Figure 10:**Acomparative analysis of the distribution of radiation doses in target volumes/ CTVand PTV/ and in the critical organs/ heart, lungs and larynx/inbothRTmethodswithfreeandretainedbreathing.Freebreathingcurvesaremarkedwithatriangleandthecurvesintheholdofthebreathing with a square.The red 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 | 0.838 | 0.325 |
| | larynx | | | | | | |
| | humerus sin | 29.2 | 100.0 | 100.0 | 0.196 | 1.270 | 0.502 |
| | humerus dex | 37.1 | 100.0 | 100.0 | 0.167 | 2.099 | 0.818 |
| | esophagus | 2.2 | 100.0 | 100.2 | 0.551 | 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 | 0.062 | 6.694 | 0.498 |
| | body | 14996.0 | 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 | 0.255 | 0.744 | 0.526 |
| | Thyroid | | | | | | |
| | RightArm | 905.9 | 100.0 | 100.0 | 0.000 | 2.726 | 0.698 |
| | RING | 833.3 | 100.0 | 100.0 | 0.249 | 24.703 | 8.195 |
| | RING | | | | | | |
| | PTVp | 112.0 | 100.0 | 100.1 | 21.618 | 26.583 | 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 |

**Figure11:**Tablerepresentingtheradiationdosesinthecriticalorgans/max,minandmean/inbothdosimetricallyplannedmethodologies.Inthefree breathingRTmethod,theyaremarkedwithatriangleandintheholdofthebreathingRTwithasquare.

## 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 ofB-cell and T-cell origin [9] They are an extremely rare kind of tumor, and they are lack of large-scale studies or definite guidelinestodescribeitsclinicalcharacteristics,treatment,andprognosis[10,11].Thethymus,locatedintheanteriormediastinum,isthe primary anatomic site of T cell development. Therefore, it is not surprisingthatmanylymphoidmalignantneoplasmsarisingwith- in 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 previ-ous studies, there were only case reports or cases series of small samplesizeforthymiclymphoma[13-16].AccordingtotheWHO classification of lymphoma, primary thymic large B-cell lymphoma(PTLBL)isthepredominantpathologicaltypeofthymiclymphoma [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/ormediastinalorgans(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 immaturelymphocytesassociatedwiththymomamayresembleT 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 MRIhasbeenusedinrecentyearssincetheimagescanbetterdistinguishthethymictumorfromneighboringstructures[25].Inthe clinical case presented from the chest CTvisualizes a retrosternal soft tissue formation 53 x 24 mm with a light -grade compression of the vena brahiocephalica. No nodular lesions/ lymphoid infiltratesarefoundinthepulmonaryparenchyma(Figure2).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 clinicalcasepresented,18F-FDGPET/CTfromMarch2022does not take into account increased metabolic activity in the retrosternaltumor(Figure3).Delayeddiagnosisandinadequateinitial therapymaycomprisethepotentialforsalvageandlong-termsurvival[26].DistinguishingbetweenthymomaandT-lymphoblastic lymphoma/leukemiamaybechallengingandrequiresmultimodalitydiagnosticapproachesusinghistological,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 associatedwiththymomamayresembleTlymphoblasticleukemia/lymphoma cells, both morphologically and immunohistochemically [20].PathologicalanalysisofT-lymphoblasticleukemia/lymphoma,showingsheetsofT-celllymphoblastspositiveforCD3,CD5, CD1a,andTdTandcompleteabsenceofepithelialcellswithnegativekeratinmarkers[27,28].Thehistologicalresultinourpatient afterthefirstbiopsyisjudgedasalymphoproliferativeprocessor 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,withoutgiantcells.Macroscopically,thethymusinvolved byHodgkin'slymphomashowmultiplefirmwhitenoduleswithor withoutvisiblefibrousbands.Onhistologicalstudy,themostcommon type is nodular sclerosis, as the other types typically affect lymphnodesexceptthethymus[29].inourpatientasecondbiopsy was required via VATS, which is a minimally invasive surgical approach. The histological result is judged as a lymphoproliferativeprocessmadeupofmonomorphiclymphoidcellswithdiffuse growth without morphologically distinct epithelial structures. A immunohistochemical examination reports CD3-positive reaction, KI 67 positive reaction above 90%, CD15 and CD20-negativereaction.Flowcytometry(FC)ishelpfulforthe classification ofnon-Hodgkinlymphoma[12].FCremainsanimportanttool 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 patientreportshyperplasticbonemarrowwithoutparablasticinfiltration,andthebonemarrowimmunoflowcytometry(IFC)doesnot identify T-lymfoblasts.Another diagnostic tool is the assessment of characteristic cytogenetic or molecular abnormalities knownto be associated with T-lymphoblastic lymphoma/leukemia, such as a monoclonal pattern of TCR-β and TCR-γ rearrangements by RT-PCRorthecharacteristictranslocationsorNOTCH1/FBXW7 mutationswhicharefrequentlyfoundinneoplasticTlymphoblasts asopposedtonormalthymocytes[32].InourpatientPCRdoesnot detectSIL-TAL1fusiongenetranscriptsandoverexpressionofthe HOX11gene.Thelumbarpuncturereportsanormalcerebrospinal liquor.Thus,thefinaldiagnosiswasmadethymicNon-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 abiopsyandnotresectivesurgery,toavoidunnecessaryresec-

tionsandmorbidity.Themaintreatmentisradiotherapy(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.WeconducteddeepinspirationbreathholdRTbytheVMAT method, which reduces the radiation dose in the critical organs near the target volume, mainly in the lungs and heart (Figure 9 and11).ThisRTmethodologyisrequiredfortheRTofmalignant mediastinal processes. In the target volumes (CTV and PTV) includingthemediastinaltumor,werealizeduptoTD25,2Gywith 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,bothinmatureandchildhood.Diagnosisisextremelydiffi- cult and requires a biopsy of the tumor and bone marrow, strictly pathohistologicalandimmunohistochemicalexamination,aswell 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 theprognosis.Prolongedtreatmentwithcorticosteroidsandaheterozygousfamily-burdenedmucoviscidosisisthecauseofsevere chemotoxicity after one course of chemotherapy. This is the reasonforthecompletionoftreatmentbyconsolidatinginvolvedsite radiotherapy.WeconducteddeepinspirationbreathholdRTtechnique by the VMAT method, which reduces the radiation dose in thecriticalorgansnearthetargetvolumes,mainlyinthelungsand heart.ThisRTmethodologyisrequiredintheirradiationtreatment of malignant mediastinal processes.

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