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Case report

Primary Thyroid Diffuse Large B-cell Lymphoma in a Child with Hashimoto's Thyroiditis: A Case Report

Xatzipsalti M et al. Primary Thyroid B-cell Lymphoma in a Child

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What is already known on this topic?
Primary thyroid diffuse large B-cell lymphoma (DLBCL) is extremely rare in children and uncommon malignancy in adults. Hashimoto Thyroiditis (HT) is a risk factor for DLBCL. Core needle biopsy is usually **required** for diagnosis.

What this study adds?
DLBCL should be considered in the differential diagnosis of a thyroid mass in adolescents with a history of HT. Diagnosis is difficult. Chemotherapy and/or radiology seems to be the most effective treatment even in children. Surgical removal of the thyroid gland is limited to cases where chemotherapy fails.

Abstract
Primary thyroid lymphoma (PTL) is a rare thyroid gland cancer, with diffuse large B-cell lymphomas (DLBCL) to be extremely rare in children and adolescents. Thus, effective therapy is debatable. We describe a rare case of thyroid DLBCL in an adolescent girl with a history of Hashimoto Thyroiditis (HT), its diagnostic difficulties and the outcome of treatment. A 12- year- old girl with known HT for the last 9 years, was admitted to our department with a right sided painless progressive swelling of the neck. Physical examination and imaging (U/S, CT, PET/CT scan) revealed an enlarged thyroid gland with right side lymphadenopathy and no metastasis. Two FNAs were done showing suspected lymphoblastic lesions for Non-Hodgkin Lymphoma without precise diagnosis. Ultra-sound guided core needle biopsy was finally performed confirming the diagnosis of DLBCL. She was treated according to LMB 96 - group B protocol with no surgical removal of thyroid. The patient responded very well to treatment and 14 months later there is no evidence of relapse or metastases. PTL is an extremely rare cause of thyroid malignancy in children However, it should be considered in the differential diagnosis of a thyroid mass in adolescents presenting with a rapidly enlarging neck mass and a history of HT. It is a treatable condition with a good prognosis even with the aggressive histological subtypes with no need of thyroidectomy.
Keywords: Primary thyroid lymphoma, diffuse large B-cell lymphoma, children

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Introduction
Studies in adults have shown that primary thyroid lymphoma (PTL) accounts for <5% of thyroid malignancies and <2% of extranodal lymphomas, with an annual estimated incidence of 2 cases per 1 million. PLT is extremely rare in children, with only a few cases documented in literature(1). We describe a 12- year- old girl with Hashimoto's disease and DLBCL.

Case Report
A 12-year-old girl was referred to our department with a painless right sided enlargement of the neck, which was observed 3 weeks prior to her admission. There was a progressive deterioration, with no other symptoms. An ultrasound elastography of the thyroid gland performed at that time showed a 3 cm hypoechoic solid nodule, with mild lobulated borders. That mass was highly suspicious of Non-Hodgkin Lymphoma, based on the fine needle

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aspiration biopsy (FNA) result, which was performed a few days before her admission. However, no definite diagnosis could be made.

The patient's past medical history was remarkable for Hashimoto's thyroiditis (HT) and she was under treatment with Levothyroxine, since the age of 2 years (Table 1). There was a family history of thyroidopathy in her two older sisters. Her elder one had also Hashimoto's thyroiditis since the age of 13 years and the eldest one had thyroidectomy at the age of 23 years because of a thyroid nodule (benign TBSRTC primary category II)

Physical examination revealed an enlarged thyroid gland with a notable soft mass (3cm x 3cm) on the right side of the thyroid and ipsilateral cervical lymphadenopathy. After admission, laboratory tests were performed. Full blood count, LDH, renal and liver function tests were all normal (Table 1). Her thyroid tests are shown in Table 1.

A more detailed ultrasound of the thyroid gland was performed and showed an increase in the size with a notable solid hypoechoic nodule (3.40x2.93x4.62cm), with two jagged edges, lobulated borders, calcifications and intranodular vascularization on the right side of the gland. Furthermore, two hypoechoic nodules, smaller in size and with well-defined borders, without internal vascularization were noticed on the left side of the gland. Multiple cervical lymph nodes were also found bilaterally. However, ultrasound was still non diagnostic. A second FNA was performed, which showed suspicious lymphoblastic lesions. Due to the difficulty of making the diagnosis, a subsequent ultrasound guided core needle biopsy (CNB) was carried out and confirmed the diagnosis (Fig 1) by histological examination.

Histopathological examination showed destruction of thyroid follicles and diffuse growth of lymphocytes (fig2,3). Immunohistochemistry stain was positive for CD20 (fig 4) with co-expression of PAX-5 transcription factor, and positive for CD5, CD23, CD30, cyclinD and moderately positive for CD3. These markers are key immunohistochemical features to distinguish between DLBCL and MALT subtypes Antibody testing against antibody/proteins CD10 < 30%, bcl-6 <30% and MUM-1/IRF4>30%. The Ki-67 index was 60%. Bcl-2 was found positive for >90% of cell population examined. FISH analysis revealed no translocation of the MYC, BCL-2, DUSP22 and IRF4 genes, indicating good prognosis (2)

Staging of the lymphoma included CT scan of the neck, chest and abdomen, Positron Emission Tomography – Computed tomography (PET - CT), bone marrow aspiration and cerebral spinal fluid (CSF) analysis.

The CT scan of the neck revealed a nodular alteration of 2.95 x 3.9 x 5.2 cm in the right thyroid gland and multiple lymph nodes in the neck bilaterally. PET/CT scan confirmed these findings with SUV max= 16.5 and 2.5 in the right thyroid gland and lymph nodes respectively. Chest and abdomen CT scans were normal. Flow cytometry, morphology and cytogenetic analysis did not show any evidence of marrow involvement and the CSF was negative for infiltration. The above findings categorized our patient into the intermediate risk group.

Due to the rarity of the disease in children, the optimal therapy (thyroidectomy or chemotherapy) was under question. Finally, it was decided to start only chemotherapy according to Lymphomes Malins B LMB 96 - group B protocol. This protocol consists of initial induction chemotherapy with COP (cyclophosphamide [300mg/m2], vincristine [1mg/m2], and prednisolone [60mg/m2—7 days]) followed by 2 courses of COPADM (doxorubicin 60 mg/m2, methotrexate 3 g/m2, cyclophosphamide 500mg/m2/day—5 days, vincristine [2mg/m2], and prednisolone [60mg/m2—5 days]) and two courses of CYM (cytarabine 100mg/m2/day—5 days and methotrexate 3 g/m2) chemotherapy. This is accompanied by intrathecal chemotherapy.

The patient responded very well to treatment with a rapid decrease in the size of the thyroid mass after COP. An ultrasound of the thyroid gland performed after completion of COP scheme revealed an 80% decrease of the size. A follow-up PET-CT scan after the first course of CYM showed that the tumor had totally disappeared. She is now disease-free 14 months after end of treatment.

Discussion

PTL is an extremely rare malignancy in children (3), representing 1-5% of all malignancies of thyroid gland in adults(3). To the best of our knowledge, this is the second case of a young adolescent with PTL reported in the literature (1).

A comparison of findings between adults and adolescents is depicted in Table 2.

Previous studies have shown that most patients were females aged 50-80 years (4-6). PTL presents with progressive swelling of the neck. Compressive symptoms (dyspnea, dysphagia, cough, hoarseness) may develop, as well as general symptoms like weight loss, night sweats and fever in 10% of the cases(7). Our patient, however, had no such symptoms (table 2). HT is a well-known risk factor for PLT with patients having a relative risk of 65 compared to those without thyroiditis (8). Our patient had a history of HT 9 years before the diagnosis of PLT (table 2). Various theories have been proposed to explain the association between HT and PTL. It has been suggested that chronic antigen stimulation of lymphocytes may lead to malignant differentiation (8). In a recent large scale-report of PTL, 154 out of 171 adult patients (90%) had Hashimoto's disease diagnosed 1-362 months prior to the diagnosis of lymphoma (9).

Many previous studies agreed that the most common subtype of PTL is diffuse large B cell lymphoma followed by mucosa-associated lymphoid tissue (MALT) lymphoma mixed type. Histopathologically, it is very important to distinguish between the above-mentioned subtypes, as therapeutic management and prognosis are different. In immunohistochemical staining, CD5, CD10 and CD23 are negative in MALT cases and CD19, CD20 and CD45 are usually positive in DLBCL (10). Most DLBCL are Bcl-6 positive and almost half are Bcl-2 positive (11). Our child found to be positive for Bc-2 and negative for MYC, DUSP22 and IRF4.

Ultrasonography (U/S) is often the first line investigation in patients with thyroid enlargement and nodules; however, its findings are sometimes non diagnostic for PTL. In the DLBCL, U/S usually shows homogenous and hypoechoic internal echoes, with indistinct borders between the lymphomatous and non-lymphomatous tissues. These findings, however, are also typical of severe chronic thyroiditis (12). In a retrospective study of 165 US-suspected patients of malignant thyroid lymphoma based on the above ultrasound findings, 79 (47.9 %) were

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confirmed as having lymphoma (12). The positive predictive value for diagnosis of diffuse type was reported lower, compared to nodular or mixed type(12).

US-FNAB (fine needle aspiration biopsy) and core needle biopsy (CNB) are the next steps for the diagnostic strategy. FNA is widely accepted for diagnostic tool due to its simplicity, safety and its high sensitivity of 83-98% and specificity of 70-92% (13). However, FNA results may be non-diagnostic in 2-24% (14). CNB has been suggested as a complimentary method to FNA. CNB is safe, well-tolerated and reduces the possibility of inconclusive results, as larger tissue sample is taken when performed by an expert. However, a recent meta-analysis by Li et al (15) found that FNA and CNB don't differ significantly in sensitivity and specificity for the diagnosis of thyroid malignancy. In our case, two FNAs and a CNB were performed to confirm the diagnosis. Previously, open surgical biopsy was necessary to differentiate lymphoma from thyroiditis and carcinoma (16). However, recent advances in immunochemistry have improved the accuracy of FNA. In 119 patients with thyroid lymphoma, Matsuzuka et al showed that only 78,3% who underwent FNA without immunotyping were diagnosed correctly, while another 12% had borderline cytologic results (16). In another study, FNA results were highly suggestive of thyroid lymphoma in only five out of 17 patients (17). Based on such studies many specialists recommended surgical intervention and open biopsy to all patients due to limited role of FNA in diagnosing thyroid lymphoma. More recent studies, however, have shown that FNA together with immunophenotyping improves the accuracy of the results. Therefore, core needle or surgical biopsies are now less often needed (18, 19). Expertise level of the physician performing the FNA, the amount of tissue taken and the pathologist's experience in interpreting FNA results are important for the accurate diagnosis. Therefore, core needle or open biopsies (to obtain enough cells) are the most preferable techniques. CNB and surgical biopsy are comparable regarding the accuracy; however, the latter is usually accompanied by trauma and possible complications (18, 19). Regarding the treatment, experience in children and adolescents is limited, since DLBCL is rare in this age group with spare data on incidence and treatment. Therefore, the optimal approach remains controversial (20). For these reasons the treatment for DLBCL is generally based on established treatment regimen for other extra-nodal non-Hodgkin's lymphomas (21). According to histology findings and cancer staging, chemotherapy, loco-regional radiotherapy and surgery could be combined for successful treatment. Surgery seems to play limited role only in large tumors with compressive symptoms (21). Surgical biopsy and resection have been used for the diagnosis and therapeutic management with significant survival benefit(21). In our case, the patient commenced on chemotherapy based on staging.

Our patient responded very well to the chemotherapy protocol with rapid decrease in the thyroid mass. The role of surgical removal of thyroid is still questionable nowadays (16). It is not a first line treatment and is limited only either to the cases that have failed to respond successfully to chemotherapy or to the cases where CNB has failed to establish the precise diagnosis (20).

The intermediate risk disease group B-NHL is the largest and most heterogeneous. In the FAB/LMB studies 70% of patients can be classified as intermediate risk (group B) and have a 4-year EFS (Event Free Survival) of 90%(20).

Conclusion

We present a case of Non-Hodgkin lymphoma which belongs to Diffuse Large B-cell Lymphomas as a primary tumor in thyroid gland, which is extremely rare in children and adolescents. The case responded very well to chemotherapy. Non-Hodgkin lymphomas should be considered in the differential diagnosis in children and adolescents presenting **with rapidly increasing**, hard, and painless mass in the neck, especially on HT background.

Statement of Ethics

All authors comply with the guidelines for human studies. Compliance with Ethics Guidelines. The patient and her parents have given their written informed consent to publish this case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author's contributions

M.X analyzed and interpreted the patient data and was a major contributor in writing the manuscript. E.B. contributed equally to the conception of the work and to the writing. M.N. participated in the treatment and contributed in writing, D.R. and M.G.G. participated in the diagnosis of the patient and contributed in writing, D.C. and A.G. participated in the diagnosis, provided clinical data and revised it critically, D.D. participated in the diagnosis and treatment of the patient and revised it critically. A.V. designed the work, intepretated the patient data, participated in the diagnosis and treatment and gave the final approval of the version to be published. All authors approved the final version.

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Age (years)	$12^{9/12}$	
sex	female	
Race	White Caucasian	
Past medical history	Hashimoto Thyroiditis since 2 years of age	
Medical Treatment	Thyroxine	
Height	155cm (50^{th} percentile)	
Weight	49kg (50^{th} percentile)	
BMI	19.38 kg/m^2 (25^{th}-50^{th} percentile)	

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Tanner stage	5	
Blood tests		Ref range
FBC:		
- WBC	6200/µl (NE: 50.2%, LY:41.1&, EO:1.3%)	4.5-13.0x10^3
- Hb	**11.1 gr/dl**	11.5-15.5
- HCT (MCV)	**34% (78.3fl)**	35-45
- PLT	308000/µl	130-400x10^3
- ESR	5mm/h	< 10
Biochemistry:		
- Urea	19mg/dl	5-45
- Creat	0.6mg/dl	0.5-1
- CRP	0 mg/dl	<5
- SGOT	11U/l	5-45
- SGPT	7U/l	5-45
- γGT	6U/l	<26
- LDH	188U/l	<300
Hormones:		
- TSH	0.603µIU/ml	0.4-5
- fT4	1.37 ng/dl	0.9-1.9
- T3	1.270ng/dl	0.83-2.13
- T4	8.15µg/dl	5.6-13.9
- Tg	**69.94ng/dl**	3.5-31.1
- Anti-TPO	**278.7IU/ml**	<16
- Anti-TG	**1287 IU/ml**	<100
- calcitonin	2.2pg/ml	<10

Table 1. Demographic, clinical and biochemical data of the patient

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	Adults	Children
Incidence	$2/10^6$ per year	2 cases
Female (F)/Male (M)	5 times more common in F	1F/1M
Rapid painless enlargement	yes	both
Compressive symptoms	common	none
Cervical lymphadenopathy	common	none
Hashimoto thyroiditis	Common (80-fold risk)	One
Ultrasound findings: -Diffuse heterogenous hypoechoic parenchyma -hypoechoic mass	 Yes (25%) Yes (67%)	 both both
Final diagnosis: -FNA -core biopsy	 Yes (50-60%) In doubtful cases	 one one
Treatment -chemotherapy and radiotherapy -surgery	 Yes no	 Both only chemotherapy none
Prognosis -survival at 5 years -survival at 10 years	 74% 71%	 Unknown (both are disease-free 2 years after diagnosis)

Table 2. Comparison between adults and children (two cases reported in literature)

Figure 1.

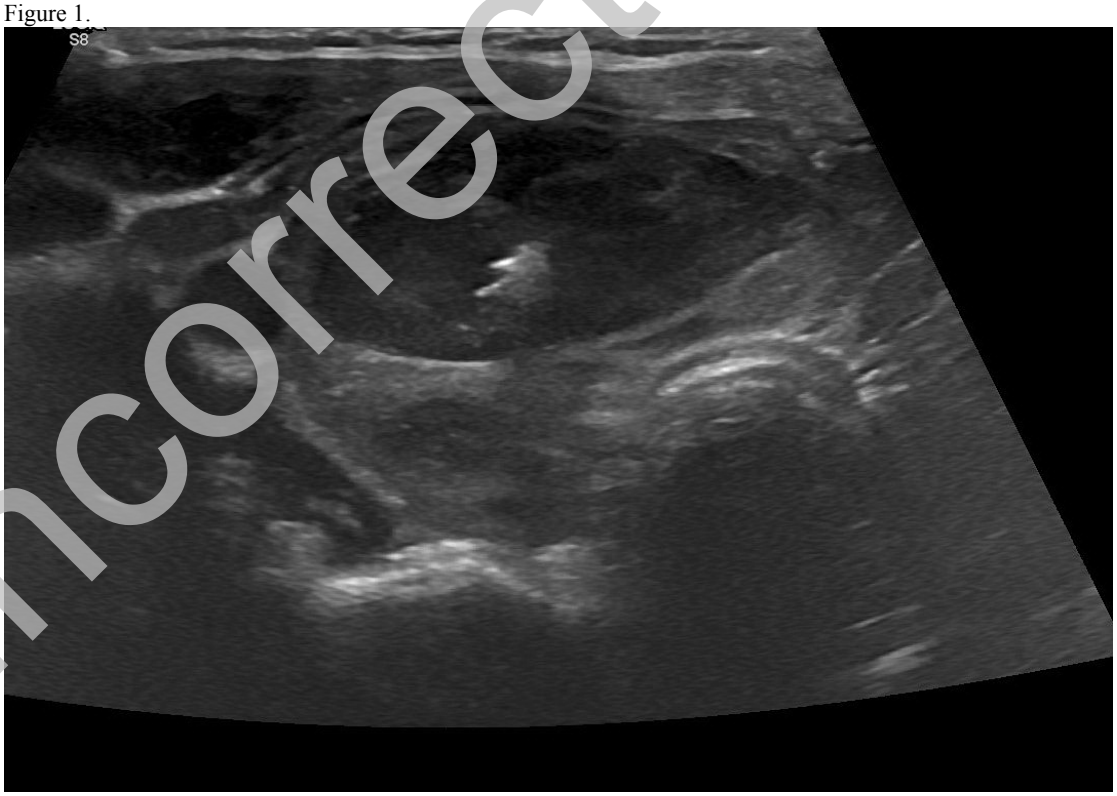

Figure 2.

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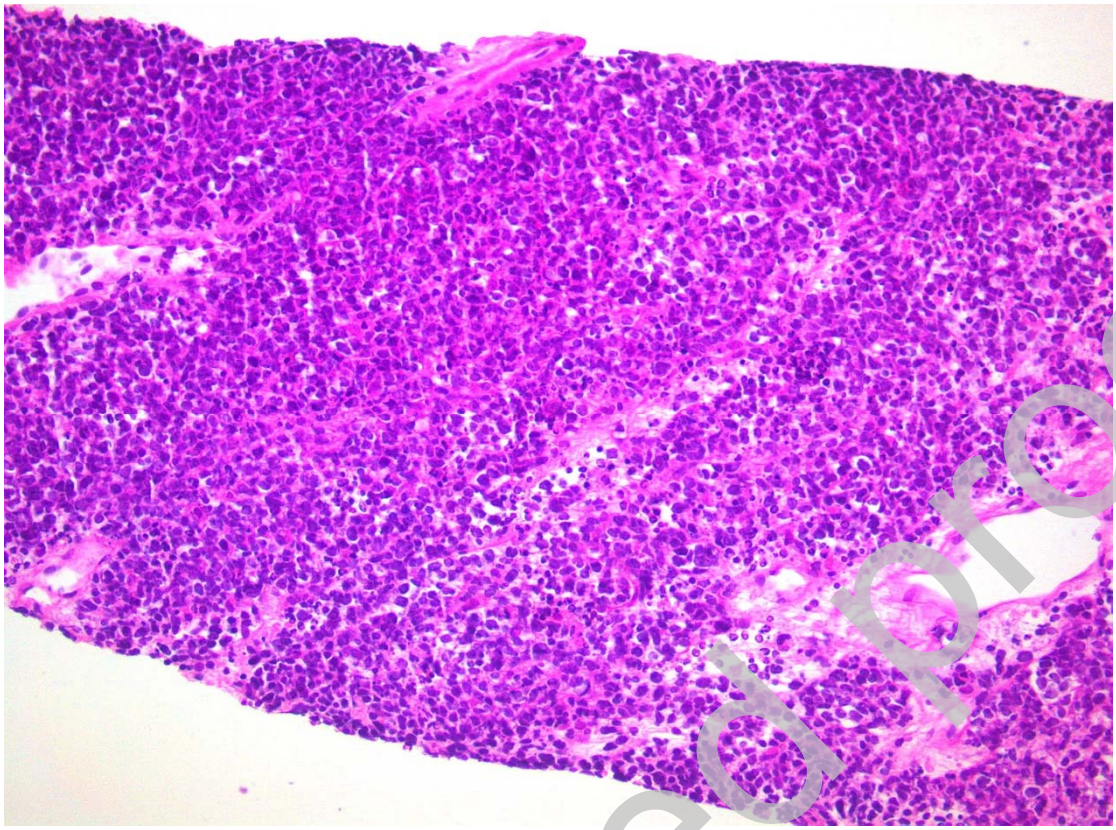

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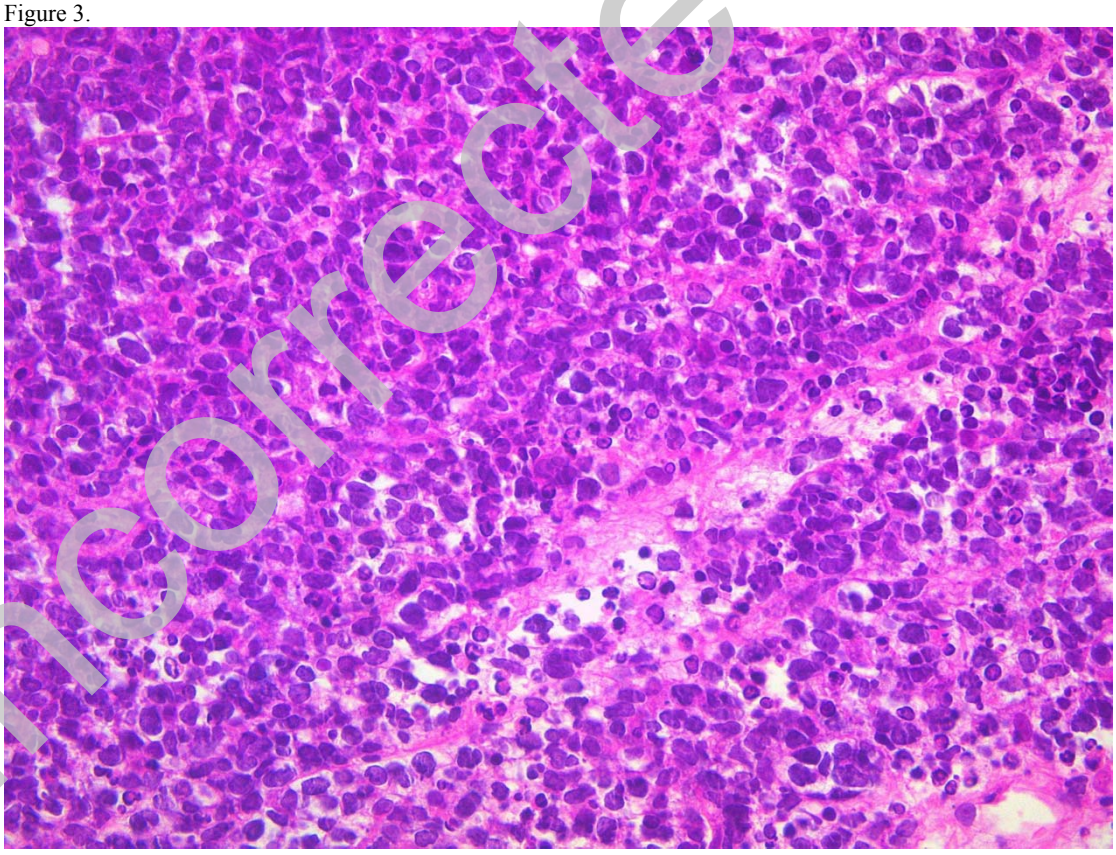

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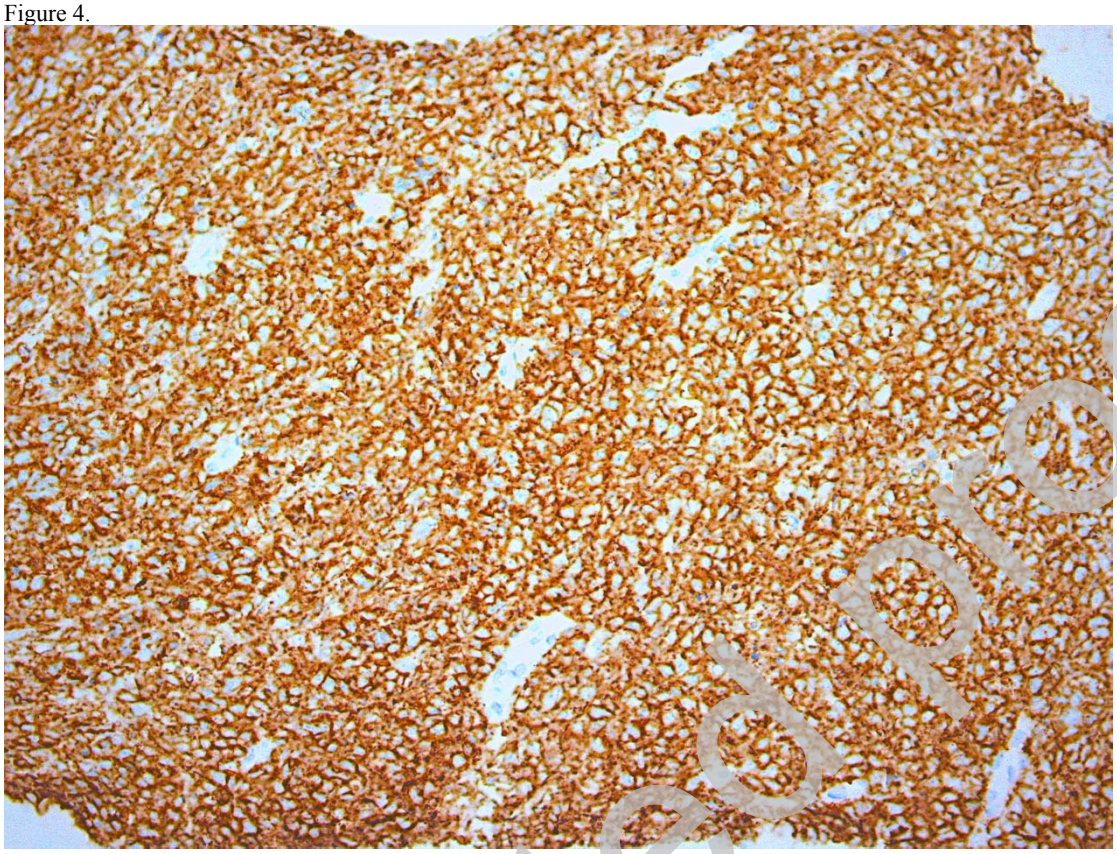
Figure 4.



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