The Prevalence of benign Lymphadenopathy in Patients with Autoimmune Thyroiditis

Johannes Meller[1], Heide Siggelkow[2], Kia Homayounfar[3], Carsten Oliver Sahlmann[1], Meral Özerden[1], Isabell Braune[1], Afshin Ghodrati[1], Gerald Kluge[1], Birgit Meller[1]

Department of Nuclear Medicine[1], Department of Gastroenterology and Endocrinology[2], Department of General and Visceral Surgery[3]; University Medical Centre (UMG); Göttingen, Germany.

Abstract:

Aim: The prevalence of cervical lymphadenopathy in autoimmune thyroiditis (AIT) patients is actually unknown. The aim of the study was the detailed *retrospective* evaluation of 6 index-patients with lymphadenopathy in Robbins level VI and a *prospective study* with high resolution ultrasound of lymphadenopathy in AIT patients compared with controls in all compartments of the neck, accessible to sonographic evaluation.

Methods: The *retrospective study* comprises six patients with AIT, evaluated for enlarged Robbins level VI-LN. We report the findings of fine-needle aspiration Cytology, clonal analysis, histology, and serological testing. The *prospective study* evaluated the prevalence of lymphadenopathy in 49 consecutive patients with AIT (group 1) and 49 consecutive patients with normal thyroids or nontoxic goiter (group2).

Results: In the *retrospective study*, cytology of paratracheal LN revealed reactive lymphoid hyperplasia in 5/6 of the cases and a centroblastic lymphoma in one patient. The presence of monoclonal lymphatic cells was excluded in 5/6 patients and proven in 1/6 patients. Actual viral-infections were ruled out. In the *prospective study* AIT-patients showed significantly more enlarged LN in Robbins level II-IV and VI compared to controls. We found no correlation between lymphadenopathy, age, thyroid volume and nodularity, or autoantibody levels. During follow-up in 21 group 1-patients, lymphadenopathy remained stable in 18 patients, and decreased in 3 patients.

Conclusion: Lymphadenopathy in Robbins level II-IV and VI is common in AIT-patients and most probably related to the autoimmune process. LN in Level VI have to be considered as pathognomonic for the disease if no other diseases of the head and neck are present.

Keywords: Autoimmune Thyroiditis (AIT), Lymph Nodes, Lymphadenopathy, Sonography.

Abstract:

Ziel: Die Prävalenz einer Lymphadenopathie (LAP) bei Patienten mit autoimmuner Thyreoiditis (AIT) ist unbekannt. Ziel der Studie war die detaillierte *retrospektive* Datenaufarbeitung von 6 AIT Patienten mit vergrößerten Lymphknoten (LKs) im Robbins Level VI und eine *prospektive Beobachtungsstudie* zur Prävalenz einer Lymphadenopathie bei Patienten mit AIT im Vergleich mit Kontrollen in allen sonographisch zugänglichen Halskompartimenten.

Methoden: Die *retrospektive Studie* umfasst 6 AIT-Patienten mit einer LAP im Robbins Level VI und beschreibt die Ergebnisse der Zytologie, Histologie, klonalen Analyse und Serologie bei diesen Patienten. Die *prospektive Studie* erfasste die Prävalenz einer LAP bei 49 konsekutiven Patienten mit AIT (Gruppe 1) und bei 49 konsekutiven Patienten mit benignen Schilddrüsenknoten oder Iodmangelstrumen (Gruppe 2).

Ergebnisse: In der *retrospektiven Studie*, wiesen 5/6 Patienten in der Zytologie eine benigne lymphatische Hyperplasie und ein Patient ein Zentroblastisches Lymphom auf. Eine klonale lymphozytäre Transformation konnte bei 5/6 Patienten ausgeschlossen und bei einem Patienten nachgewiesen werden. Virale Infektionen wurden serologisch bei allen Patienten ausgeschlossen. In der *prospektiven Studie* waren Patienten aus Gruppe 1 signifikant jünger, hatten ein signifikant niedrigeres Schilddrüsenvolumen und wiesen signifikant häufiger eine LAP im Robbins Level II-IV und VI auf. Eine Korrelation zwischen LAP, Alter, Schilddrüsenvolumen, Nodularität und Höhe der Autoantikörper lag nicht vor. Eine Nachkontrolle erfolgte bei 21 Gruppe-1 Patienten. Die LAP zeigte bei 18 Patienten einen identischen und bei 3 Patienten einen regredienten Verlauf.

Schlussfolgerung: Eine LAP im Robbins Level II-IV und VI wird bei AIT Patienten häufig gefunden. Dieser Befund scheint direkt mit dem Autoimmunprozess assoziiert zu sein. Eine LAP im Robbins Level VI kann als pathognomonisch für eine AIT angesehen werden, wenn andere Erkrankungen des Kopf-Halsbereiches ausgeschlossen sind.

Keywords: Autoimmunthyreoiditis (AIT), Lymphknoten, Lymphadenopathie, Sonographie.

Corresponding Author: Johannes Meller, MD, Georg August University Göttingen, Centre for Radiology; Department of Nuclear Medicine; Robert-Koch-Str. 40 37075 Göttingen Tel: 0551/39-8510; FAX: 0551/39-8526. E-Mail: jmeller@med.uni-goettingen.

Introduction:

Autoimmune thyroiditis (AIT) is the most common organ specific T-cell mediated autoimmune disease, characterized by diffuse lymphocyte infiltration and reactive fibrosis of thyroid tissue (2,5,6). AIT may be followed by hypothyroidism in roughly 30% due to progressive depletion of thyroid epithelial cells and is occasionally associated with other autoimmune diseases such as Sjögren's syndrome, type I Diabetes and Addison's disease (7). Diagnosis is made by determination of elevated antibodies against thyroid peroxidase and thyroglobulin, and a typical pattern on ultrasound (5).

The sonographic findings of autoimmune thyroiditis include nonhomogeneous echotexture, hypoechogenicity of the parenchyma and lobulation of the thyroid by hyperechoic interlobular septa (7). Hypoechoic micronodulation of the thyroid has also been described, using high resolution ultrasound (14). In Middle Europe goiter in AIT is an infrequent finding, while atrophic AIT is more common (7,8). Up to 20-30% of patients present with a sonographically normal thyroid and/or antibody negativity (7,8).

In addition to these sonomorphological characteristics of the thyroid itself, an increased prevalence of enlarged cervical lymphatic nodes (LN) in patients with autoimmune thyroiditis has occasionally been reported in endocrinologic textbooks and overviews (5). In particular, involvement of the Delphian node cranial to the thyroid isthmus may be associated with immunothyreopathies and can be confused with an intrathyroidal node by clinical examination (5). There is only 1 retrospective sonographic study investigating the prevalence of enlarged paratracheal LN and the authors detected significantly more often enlarged paratracheal lymphatic nodes in patients with AIT compared to controls (11).

On the other hand, lymphoproliferative diseases (low-grade B-cell lymphoma of mucosa-associated lymphoid tissue [MALT]) and papillary thyroid cancer (PTC) have been found to be associated with autoimmune thyroid diseases (3,4). Therefore patients with AIT and enlarged lymph nodes of the neck need particular clinical attention.

Between 2006 and 2011 six AIT patients of our thyroid outpatient clinic were extensively investigated for their enlarged paratracheal LN, to rule out Non-Hodgkin lymphoma (NHL) or metastatic spread of PTC. In this context the scare literature for the incidence of enlarged cervical LNs in AIT was screened. We found that the real incidence of lymphadenopathy in AIT patients was actually unknown. The aim of the present study was the evaluation of the results in our 6 index-patients (part 1, retrospective study) and a prospective study (part 2) of lymphadenopathy in AIT patients compared with controls in all compartments of the neck, accessible to sonographic evaluation.

Methods

Part 1 of this study has a retrospective design and comprises six autoantibody positive patients with AIT (female: n=5, male: n=1; median age 35 yrs.; range: 19-75 yrs.), evaluated for enlarged paratracheal LN by high resolution ultrasound (HD11 XE Ultrasound System; fitted with a 5-13 MHz linear transducer; Philips Deutschland; Hamburg; Germany) in our institution during 2006-2011. Fine-needle aspiration cytology (FNAC) was performed in all patients. When FNAC detected lymphoid hyperplasia, further investigation of the specimen by IGH Gene Clonality Assay was performed (IdentiClone™, InVivoScribe Product Group).
Infection with Borellia Burgdorferi and Cytomegaly virus (CMV) were serologically evaluated in all patients, but 5 patients consented to additional screening for infections with Epstein Barr Virus (EBV), Herpes simplex virus (HSV), Toxoplasmosis and Human immunodeficiency virus (HIV). A white cell blood count and the determination of CRP were performed in all patients.

Part 2 of this study is a prospective investigation of consecutive patients of our thyroid outpatient clinic performed between 10/2011 and 2/2012. A single well experienced physician (J.M.) who was blinded to actual laboratory findings performed all the ultrasound examinations and prospectively documented the sonographic results. Laboratory findings were added to the database several (2-5) days later. Patients with AIT (Group1; n=49) were defined by the presence of autoantibodies against the thyroid peroxidase (anti-TPO) determined by an electrochemiluminescence assay (ECLIA) with a cut-off limit for positivity of 34, 0 kIU/l and (subclinical) hypothyroidism (TSH > 3 µU / l) or by a hypoechoic thyroid combined with (subclinical) hypothyroidism. Autoantibody negative patients with benign thyroid nodules or non-toxic goiter served as controls (Group 2; n=49). We excluded patients

with an actual cold common disease, a history of ^{131}I-therapy, head and neck cancer, external beam radiation therapy of the neck and cervical surgical intervention within the last 6 months. B-Mode Ultrasound and Power Doppler sonography (PDS) of the neck were performed with a Siemens ACUSON Antares ultrasound scanner fitted with a 5-13 MHz linear transducer (Siemens Deutschland; Erlangen, Germany). A normal echogenicity of the gland was assumed if the echogenicity of the thyroid was higher than the echogenicity of the cervical muscles. A decreased echogenicity was assumed if the echogenicity of the thyroid visually resembled the echogenicity of the cervical muscles. A nodular thyroid was assumed if at least one thyroid nodule>1 cm was present. For this study the lymph nodes of the neck were divided into 4 compartments. Compartment 1 (Robbins level I): submental and submandibular lymphatic nodes. Compartment 2 (Robbins level II-IV): jugulodigastric, middle jugular and low jugular nodes. Compartment 3 (Robbins level V): posterior triangle nodes. Compartment 4 (Robbins level VI): prelaryngeal / pretracheal lymphatic node from the inferior margin of hyoid to manubrium sterni (9). A compartment was considered as positive if more than 5 lymphatic nodes larger than 5 mm in the transversal axis were present (compartment 1-3), while the mere presence of at least one lymphatic node in compartment 4 defined its positivity. PDS was only performed in LN with a short axis/long axis [S/L] ratio > 0.5. 21 patients from group 1 had follow up by sonography after median 13 (range 10-16) weeks.

Statistical analyses were performed using PASN Statistics 18 (SPSS Inc.) and nonparametric tests. The Mann-Whitney as well as the Kruskal-Wallis test was used to compare independent samples. P-values <0.05 were considered significant.

Results

Part 1, retrospective study: All 6 patients showed the typical features of AIT on ultrasound and had 2-9 lymphatic nodes > 5mm in the fourth compartment. (median transversal diameter: 1,4 cm; range: 0,9-2,2 cm) The incidence of LN in other compartments was not systematically reported. FNAC of the LN revealed reactive lymphoid hyperplasia and centroblastic lymphoma in 5 and 1 patient, respectively. The presence of monoclonal lymphatic cells could be excluded in 5/6 patients and was proven in 1/6 patients by the IGH Gene Clonality Assay. White cell blood count and CRP levels in all patients were within the normal range. Actual infections with CMV, EBV, HSV, Toxoplasmosis, HIV and Borellia

Burgdorferi were ruled out in 5/6 patients, while 3 patients had serological evidence of EBV infection in the past. One patient with enlarged LN in Robbins level VI revealed widespread microcalcifications of both thyroidal lobes. This patient underwent surgery. Bilateral diffuse sclerosing PTC was diagnosed by histology. 4/4 LN from Compartment 4 showed lymphatic hyperplasia without metastatic disease in this case. Examples of the sonographic findings are displayed in Figure 1-6.

Part 2, prospective study: 39/49 (79%) of group 1- patients showed the typical features of AIT on ultrasound. Hypoechogenicity of the thyroid was absent in all group-2 patients. *Table 1* shows the basic clinical characteristics and the number of positive compartments for each group. There was a significant difference in age, thyroid volume and enlarged LN in compartment 2 and 4 (Robbins level II-IV and VI) between group 1 and group 2. LN with [S/L] ratio >0.5 were only present in group-1 patients in compartment 4 and had no hypervascularity on PDS. Calcifications and intranodal cystic necrosis were not observed in any of the LN. During follow-up in 21 patients, lymphadenopathy persisted or regressed in 18 and 3 patients group 1- patients, respectively.

No significant correlations between single compartment positivity and age, thyroid volume or nodularity could be detected in group 1 and 2. Sensitivity and specificity to detect AIT was further calculated for those LN compartments that showed significantly more LN in group 1 (compartment 2 and 4). While sensitivity for compartment 2 and 4 was 48% and 45% respectively, a specificity of 88% and 96% was calculated. However, when summing up the positivity of all 4 compartments the median value in group 1 was significantly higher compared to group 2 (median 2 (range 0-4) versus median 0 (range 0-4), $p<0.001$).

In group 1 TPO-values ranged from <34 kIU/l (cut-off, n=15) to 2784 kIU/l. In order to evaluate the impact of TPO antibody values on compartment positivity, patients were trisected into nearly equal subgroups (Sg 1: TPO < 34 kIU/l (cut-off level, n =15) Sg 2: TPO 34-150 kIU/l (n=15), Sg 3: TPO >150 kIU/l (n=19)). Using the Kruskal-Wallis test for independent samples no significant differences between the subgroups could be detected.

Discussion

Our publication is the first that describes prospective data about the incidence and extend of hyperplastic lymphatic nodes in all cervical compartments accessible to high resolution ultrasound in AIT patients. Our results strongly suggest that a specific pattern of lymphatic involvement exists in AIT. Regarding the sites of lymphadenopathy, we found that enlarged lymph nodes of the cricothyroidal and pretracheal / infrathyroidal compartment were almost selectively found in AIT-patients and have to be considered as pathognomonic for the disease in the absence of head and neck cancer. Our study confirms retrospective data published by Serres-Creixams and coworkers, who reported that enlarged paratracheal lymphatic nodes (Robbins level VI) were significantly more often present in patients with AIT compared to controls (11). In addition we found that LN of Robbins level II-IV were also more often enlarged in AIT, thus extending the earlier observations in this subject. The sensitivity of enlarged LN in Robbins level VI in our study for diagnosing AIT was lower than in the patients of Serres-Creixams and coworkers (45 vs. 93,4%), which may be mainly explained by the prospective character of our study and a different definition of LN-positivity. In addition, patients cohorts may differ between a university clinic and a tertiary care university-affiliated hospital (11). Anyhow the specificity of enlarged LN in Robbins level VI for the presence of AIT is reproducible high, if no other diseases of the head and neck are present (Fig. 1, Fig. 2, Fig. 3).

High resolution real time ultrasonography is able to detect LN with minimum axial diameters of 1-2 mm. The cut-off of 5 mm for *LN-positivity* used in our prospective study is somewhat arbitrary and in the lower range of cut-off points for normal nodal size in oncological studies of the neck using high sensitivity diagnostic approaches (12). The cut-off points for *compartment positivity* were also arbitrary chosen and took into consideration, that compared to other compartments, visible LN in Robbins level VI are rare (12).

In some individuals paratracheal LN adjacent to the lower thyroidal pole could not be easily distinguished from other lesions, in particular parathyroid adenoma (Fig. 4, Fig. 5). In these cases the determination of parathyroid hormone and blood calcium levels helped to establish the diagnosis. In our patients, extensive lobulation of the thyroid sometimes mimicked enlarged hypoechoic lymph nodes, which required a subtle dynamic multiplanar

sonographic technique in differentiating the two conditions. For unknown reasons, inflammatory paratracheal LN often had a [S/L] ratio > 0.5, and should not be confused with metastatic disease. In these cases the normal vascularity on PDF confirms the benign character of the lesions. As already noticed in the retrospective group of index-patients, involvement of the Delphian node occasionally required cytological confirmation, because the differentiation from a hypoechoic intrathyroidal lesion was crucial (Fig. 3). In most of these patients, the pattern of an ovaloid hypoechoic lesion with hyperechoic margins within the ventral circumference of the isthmus was indicative for a LN (Fig. 1, Fig. 2).

One index-patient of our retrospective study presented with a hypoechoic nodule in the left lobe of the thyroid and with slowly growing LN in Robins level II-VI (round appearance; axial diameter < 1 cm) during follow-up. Cytology and clonal analysis was suspicious for a thyroidal B-NHL with involvement of the LN. Histology revealed a centroblastic lymphoma.

Primary thyroid lymphomas (PTL) constitute less than 1% of all NHLs and typically arise in the setting of AIT. Lymphocytic thyroiditis is associated with a 50 fold risk for MALT-lymphoma compared with controls. On average it takes 20-30 years for PTLs to develop after the onset of the autoimmune inflammatory process of the thyroid (3). In Diffuse Large Cell lymphomas (DLBCL), a short history of a rapidly growing neck mass is always present. On the other hand, MALT-lymphomas and other slow growing NHLs show a more indolent course and the sonographic differentiation of an incipient intrathyroidal lymphoma within a lobulated hypoechoic thyroid may be crucial. Regional lymph nodes may be affected by PTLs and should be taken into account in patients with AIT, if the pattern of lymphadenopathy changes (3).

Patients with PTC have a high incidence of LN-metastasis, even in patients without clinical suspicion. As recently shown, cervical occult lymph node metastasis in cN0 papillary thyroid carcinoma mainly localizes in level VI and level II-IV (13). In patients with associated AIT it may be impossible to differentiate LN with metastatic load from LN involved in the autoimmune process by sonography. In one of the index-patients there were several suspicious paratracheal LN with a [S/L] ratio > 0.5, but histology excluded malignancy in this case. The most specific features for LN involvement in PTC remain microcalcifications and cystic degeneration, provoked by intranodal necrosis (10), not present this patient.

Our data could indicate either that lymphadenopathy in patients with AIT is more common compared to controls due to an increased “susceptibility” to viral infections or indicate that lymphadenopathy in AIT-patients is an inherent part of the autoimmune disease. Several lines of evidence suggest that viral infections cannot explain the sonographic findings, as we had no serological proof for actual viral infections in the retrospective cohort and excluded patients with clinical signs of infection from the prospective cohort.

In turn, the preferential pattern of lymphadenopathy in AIT-patients may be sufficiently explained by the immunogenetics of the disease (2). In humans and different animal models, AIT starts with the accumulation of major histocompatibility complex (MHC) class II-positive antigen-presenting cells (APCs), particularly dendritic cells, and different subclasses of macrophages, in the thyroid. APCs present thyroid-specific autoantigens to T cells, which in turn leads to T-cell activation and clonal expansion. Indeed, there is also ample evidence that the thyroid cell itself, by expressing MHC class II-molecules, can play the role of APCs and presents the autoantigens directly to the T cells (2)

This early phase of disease is followed by a clonal expansion phase and by the maturation of autoreactive T and B lymphocytes in the draining lymph nodes (2; Fig. 6). It seems reasonable to ascribe lymphadenopathy in Robins level II-IV and VI in AIT-patients to this mechanism, which is present early after initiation of the disease. If lymph node involvement of AIT decreases with time, remains a matter of debate (11). In the prospective cohort of our study it was almost impossible to determine the clinical onset of disease and therefore we were not able to correlate duration of disease and the presence and absence of lymphadenopathy. In addition, contrary to the retrospective data of Creixams et al., we found no age dependency of lymphadenopathy in AIT-patients and the controls. The interplay between intrathyroidal pathology and lymph node involvement during the clinical course of AIT certainly deserves further evaluation both on a molecular and a clinical level.

Conclusion:

Lymphadenopathy in Robbins level II-IV and VI is common in AIT-patients and most probably related to the autoimmune process. LN of the cricothyroidal and pretracheal / infrathyroidal compartment have to be considered as pathognomonic for the disease if no other diseases of the head and neck are present. Physicians should keep in mind the typical features of this

condition in order to avoid misdiagnosis in the context of possible associations between AIT, PTC and thyroidal NHLs.

Tables

Table 1: Basic clinical characteristics and number of positive compartments group-1 and group-2 patients

	Group1	**Group2**	**Significance***
Sex	5 m, 44 f	7 m, 42 f	n. s.
Age	32 (16-73) years	51 (15-87) years	<0.001
Thyroid volume	12 (8-20) ml	25 (5-130) ml	<0.001
Nodularity	n = 16	n = 36	<0.001
Co. 1 positivity	16	12	n. s.
Co. 2 positivity	24	6	<0.001
Co. 3 positivity	14	12	n. s.
Co. 4 positivity	22	2	<0.001

Table 1: Values for age and thyroid volume are displayed by median and ranges, Co= compartment, *Mann-Whitney-U-test for independent samples.

Figures

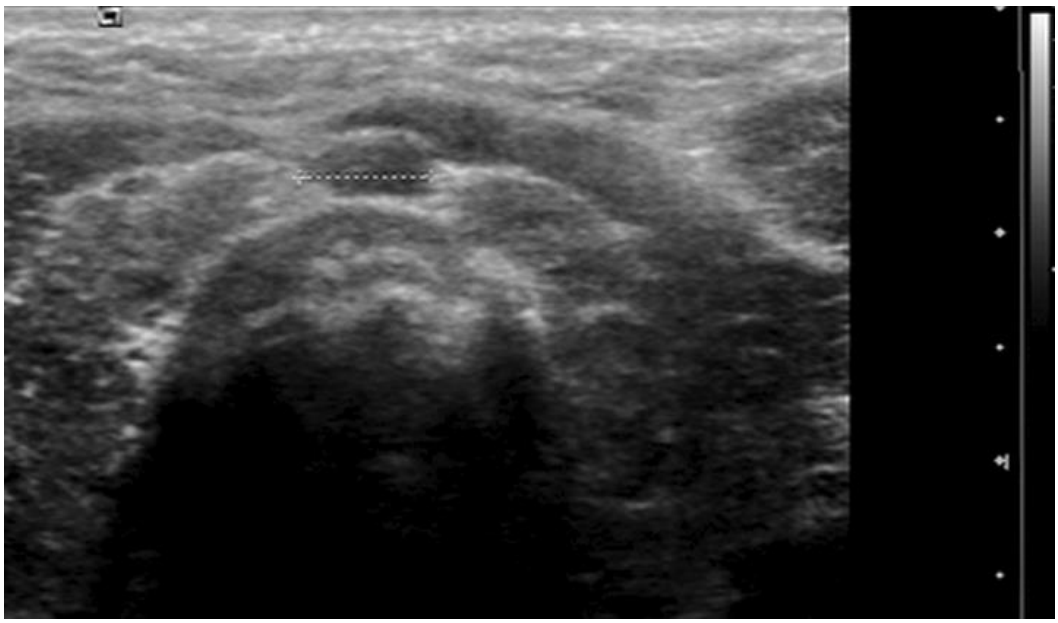

Figure 1: Median Delphian LN in AIT (transaxial view, cytology: lymphoid hyperplasia.) Note the typical pattern of an ovaloid hypoechoic lesion with hyperechoic margins within the ventral circumference of the isthmus, also seen in Figure 2.

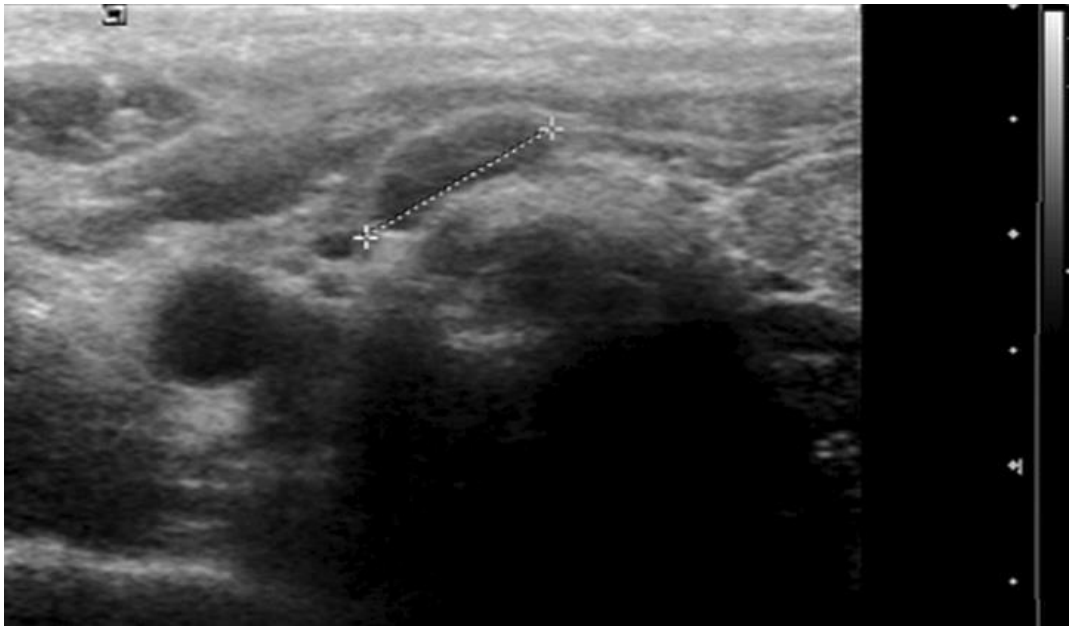

Figure 2: Paramedian Delphian LN in AIT (transaxial view, cytology: lymphoid hyperplasia)

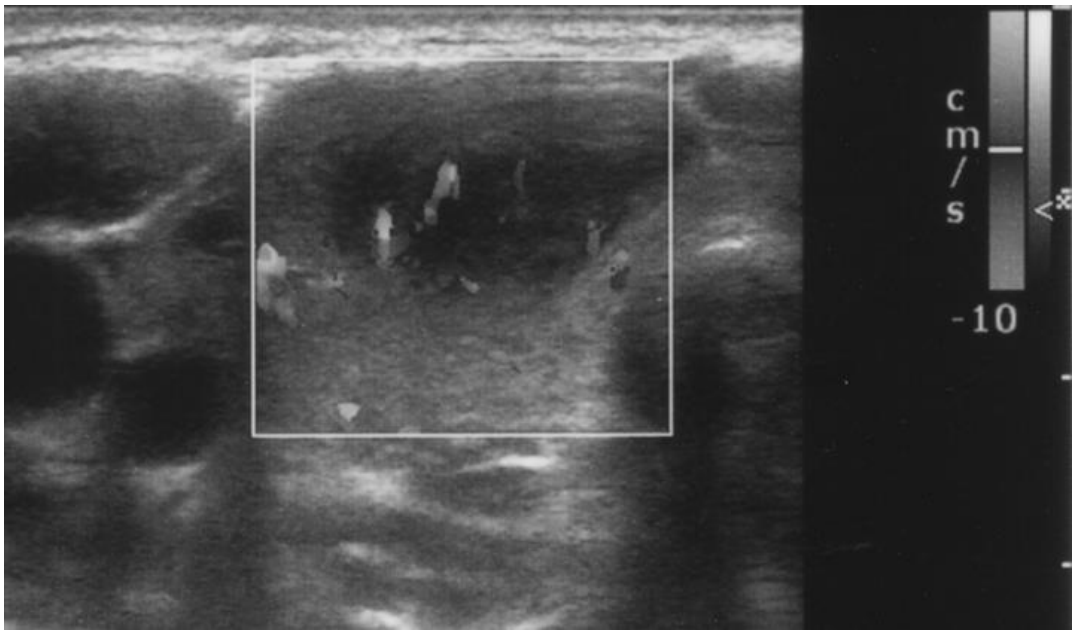

Figure 3: Delphian LN in AIT with the appearance of an intrathyroidal nodule (transaxial view, PDS: hyperemia; cytology: lymphoid hyperplasia)

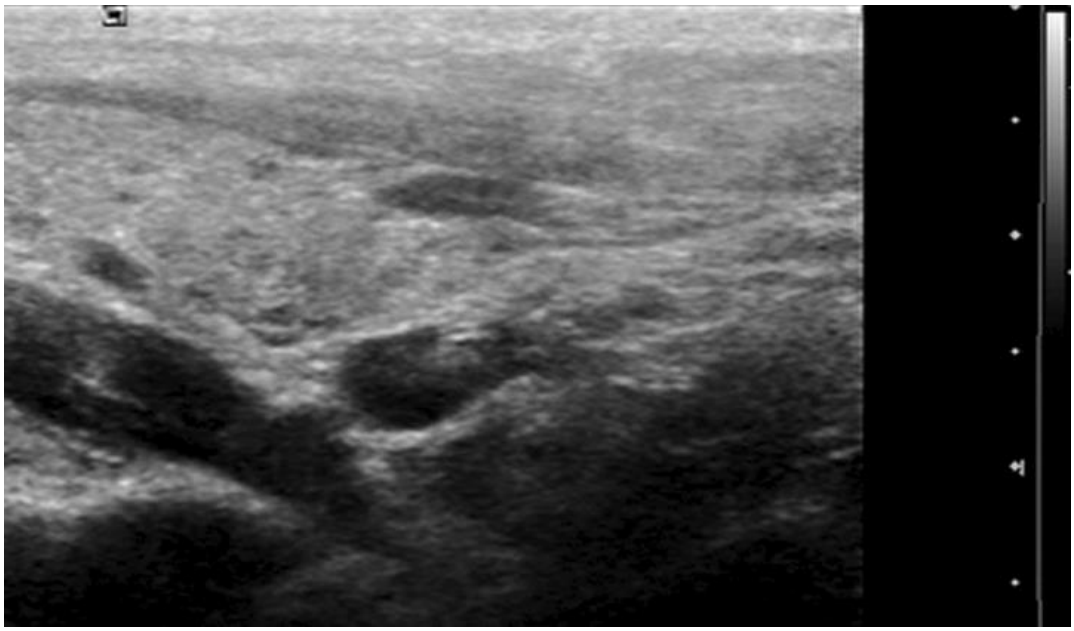

Figure 4: Lymphadenopathy of the lower thyroidal pole; Robbins level 6: (longitudinal view). Hyperparathyroidism was subsequently ruled out.

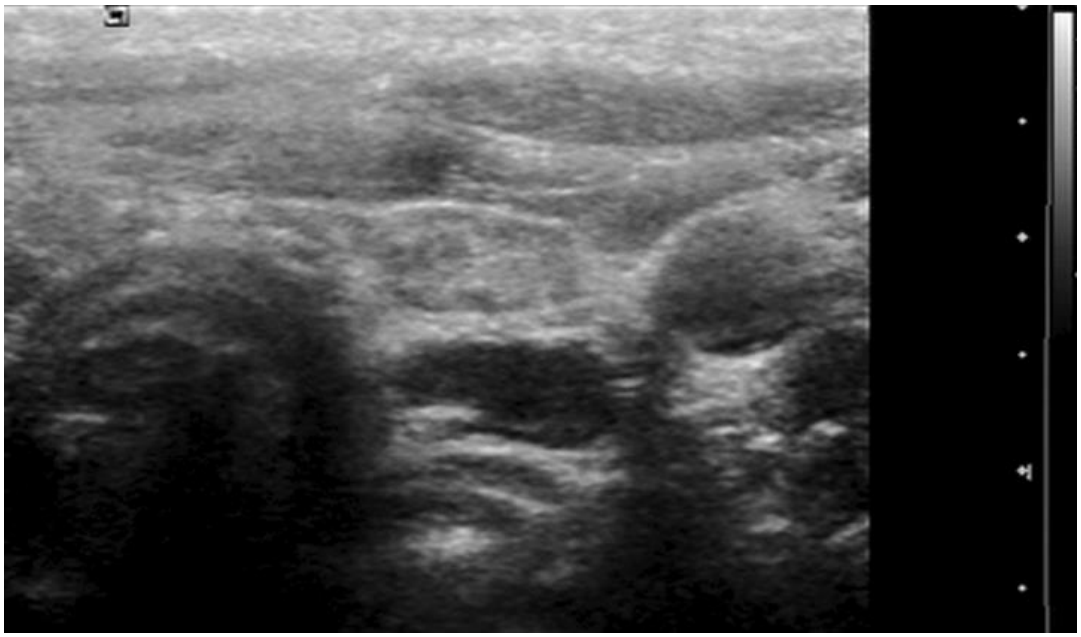

Figure 5: Lymphadenopathy of the lower thyroidal pole; Robbins level 6: (transaxial view). Hyperparathyroidism was subsequently ruled out.

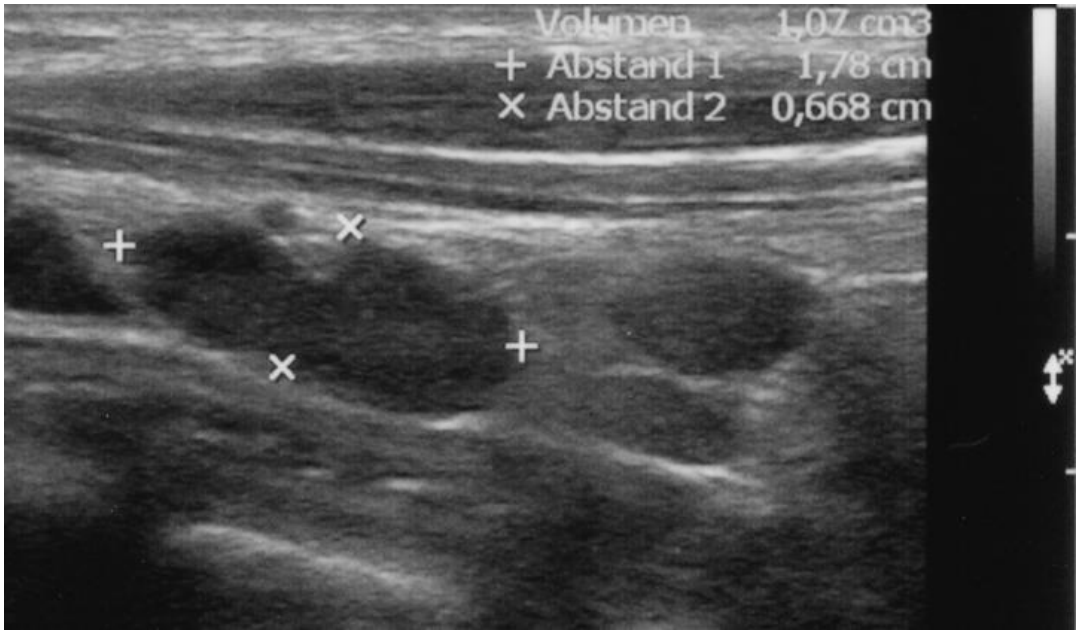

Figure 6: Lymphadenopathy of Robbins level 6 in AIT (longitudinal view)

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