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Thyroid Dysfunction in Mycosis Fungoides: Sonographic and Laboratory Insights

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ABSTRACT

Introduction: Thyroid gland affection in mycosis fungoides has rarely been reported. It occurs as extracutaneous involvement, incidentally, as a second malignancy, or as a side effect of systemic retinoids.

Objective: This study aimed to specifically screen for biochemical or structural thyroid gland affection in a larger number of mycoses fungoides patients.

Methods: Twenty-eight mycosis fungoides patients received a formal thyroid ultrasound examination, and their thyroid hormones and anti-thyroid peroxidase antibody levels were evaluated.

Results: Hypoechogenic thyroid gland (suggesting thyroiditis) was detected in 39.3% of patients, and 39.3% had thyroid nodules. Thyroid hormones and anti-thyroid peroxidase antibodies were normal in 92.9% of patients. There was a statistically significant relationship between the mycosis fungoides variant and glandular echogenicity. Eighty percent of patients with the hypopigmented variant had hypoechoic gland, compared to 43.8 % of patients with the patch stage and none of the patients with the poikilodermatous variant (P=0.017*). There was a statistically significant relationship between the mycosis fungoides variant and DTD-TIRADS score (P=0.014*). The mean duration of mycosis fungoides was longer in patients with DTD-TIRADS III and IV and with thyroid nodules, however, without statistical significance. Patients treated with systemic psoralen ultraviolet A phototherapy, compared to narrow-band ultraviolet B phototherapy, were more likely to have thyroiditis, however, without statistical significance (P=0.265).

Conclusions: We recommend regular screening for thyroid gland affection in mycosis fungoides patients because of the possible association with thyroiditis and thyroid nodules, especially in patients with the hypopigmented variant.

Introduction

Mycosis fungoides (MF) is an indolent primary cutaneous T-cell non-Hodgkin lymphoma. It classically presents with scaly patches, mainly over covered body sites. It progresses slowly from patch stage to plaques and tumors only in a subset of patients. Extracutaneous involvement is uncommon, occurs mainly in advanced stages of the disease, and may carry a fatal outcome [1,2]. However, classically, MF has a rather benign course, with an 88% 5-year survival rate [3]. Patients are typically adults aged 55 to 60 years, and MF affects males more than females, with a ratio of 2:1 [4]. In addition to the more classical presentations of MF, other clinical variants exist. These include the folliculotropic MF, hypopigmented MF, ichthyosiform MF, and poikilodermatous MF. Despite their different clinical presentations, they share the main histopathological features as the more classical types [2,5,6]. Imaging is extremely important in the evaluation of any newly diagnosed case of MF for the purpose of staging and the evaluation of extracutaneous disease, and especially important for the search of lymphadenopathy and hepatosplenomegaly [7]. In advanced stages of the disease, a number of other internal organs may be affected, such as the bone marrow, lungs, gastrointestinal tract, kidneys, thyroid gland, pancreas, and heart. There are even case reports of involvement of the larynx, oral cavity, oropharynx, and the paranasal sinuses [4,8]. Thyroid gland affection in patients with MF has been reported only in a few case reports, either as part of extracutaneous dissemination or as associated T-cell mediated thyroiditis (Hashimoto thyroiditis), as a second malignancy, or finally because of the systemic retinoid bexarotene [9-11].

Objectives

This study aimed to detect all possible forms of thyroid gland affection, biochemical or sonographic, in a group of MF patients by conducting a formal thyroid gland evaluation.

Methods

This study was carried out on 28 patients presenting with biopsy proven primary cutaneous T-cell lymphoma (mycosis fungoides) at the Dermatology Outpatient and Phototherapy Clinics at our main university hospital. The study was approved by the local Ethics Committee, and all procedures were performed in accordance with the Helsinki Declaration of 1975, revised in 2000. Written informed consent was obtained from all the patients. Patients included were of either sex, aged ≥18 years. Patients' history was obtained, including age, age at onset, duration of MF, and progression of the disease. Examination was performed to assess the current presentation of MF. The histopathological reports of the patients were reviewed from the patients' files, as were received treatments and baseline and follow-up laboratory investigations and imaging. All patients underwent sonographic screening of their thyroid gland. Thyroid hormone profile was assessed to evaluate the thyroid gland function, in addition to the serum anti-thyroid peroxidase antibody level to assess the presence of autoimmune thyroid disorder, mainly Hashimoto thyroiditis.

Thyroid Function Laboratory Evaluation

For all patients, we measured serum thyroid hormones levels by immunoassay, namely the thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4).

For the evaluation of serum anti-thyroid peroxidase (TPO) antibodies, 5 ml of venous blood was obtained from each subject by venipuncture. Serum samples were collected by centrifugation of blood samples at 3000 rpm for 10 minutes. Levels of TPO antibodies were determined in serum samples by enzyme linked immunosorbent assay (ELISA). Serum samples were tested with a commercial ELISA kit (BT Lab; Bioassay technology laboratory, China). The standard curve range was 0.5-100 ng/ml, and the sensitivity was 0.24 ng/ml. Briefly, 50 µl of standard was added to each standard well of a 96-well plate, 40 µl of sample was added to each sample well followed by 10 µl of biotinylated TPO antibody. Then 50 µl of streptavidin HRP conjugate was added to both sample and standard wells. The mixture was incubated for 60 minutes at 37° C. To remove excess unbound antibody, 300 µl of washing buffer was added to all wells. Following the washing step, 50µl of substrate A and substrate B were added to each well, then the plate was incubated for 10 minutes at 37° C in the dark. Finally, 50 µl of stop solution was added to each well, and the blue color changed into yellow. Optical density (OD value) of each well was determined using ELISA reader set to 450 nm.

Thyroid Ultrasound Scanning

High-resolution ultrasound (US) scanning was performed on all patients using the linear prob through the transverse and longitudinal gray-scale and color Doppler US images to assess the thyroid parenchyma. The following US features were investigated: echogenicity of thyroid parenchyma (normal, decreased, or increased compared with the strap muscle and adjacent fat tissue as the reference), echotexture (homogenous or heterogenous), anteroposterior diameter (APD) of the thyroid gland (normal, 1–2 cm; increased, >2 cm; or decreased, <1 cm), glandular margin (smooth or lobulated), presence of thyroid nodules (with full description), and parenchymal vascularity (normal, decreased, or increased) [12]. A thyroid imaging reporting and data system (TIRADS) with sonographic risk stratification was used to assess the

risk of malignancy of thyroid nodules (ACR classification) [13] and presence of thyroiditis in thyroid parenchyma (DTD-TIRADS) [14].

Sample Size Estimation

Sample size was calculated using Epi Info-7 program [15] by adjusting power at 80%, 95.0% confidence level (CI), and prevalence of thyroid dysfunction among MF patients 1.8% [9]. The minimum estimated sample size was 27 patients. The following formula was used: S= Z2 × P × (1–P)/M2, where S = sample size for infinite population, Z = Z score (1.96); P = population proportion (0.018), and M = margin of error (0.5).

Statistical Analysis of the Data

Data were entered into the computer and analyzed using IBM SPSS software package version 25.0. Qualitative data are described using number and percentage. The Kolmogorov-Smirnov test was used to verify the normality of distribution; data were not normally distributed. Quantitative data are described using range (minimum and maximum), mean, standard deviation, and median. Significance of the results obtained was judged at the 5% level. The tests used were the Mann-Whitney test, chi-squared test, and the Kruskal-Wallis test.

Results

This study included a total of 28 patients (19 females and 9 males). The patients' ages ranged from 18 to 75 years, with a mean of 46.93±15.93 years. Sixteen patients presented with classical patch stage MF, five with the hypopigmented variant, and seven with the poikilodermatous variant. The mean disease duration was 4.68±4.74 years, ranging from one to 20 years. The mean age for the hypopigmented type of MF (42.20±19.33 years) was younger than that for the poikilodermatous (43.0±12.49 years) and patch stage MF (50.13±16.41 years). Patients with the patch stage MF were older than in the other two types. However, the age distribution amongst the MF types was not statically significant (*P*=0.495). All three types of MF were more common amongst our female patients, but this is probably attributed to the higher number of female patients in our study. All patients were receiving skin-directed therapy, in the form of narrow-band ultraviolet B (NB-UVB) phototherapy in 14.3% of patients and systemic psoralen and ultraviolet A (PUVA) phototherapy in 85.7% of patients. All patients underwent routine laboratory investigations prior to initiating the skin-directed therapy. These included complete blood count and blood film, when indicated, and liver transaminases, urea and creatinine levels, and lactate dehydrogenase. Values were all within normal range in all study patients. Imaging was also performed at the time of diagnosis for the purpose of staging. Fifteen patients received ultrasound examination of abdomen and pelvis for detection of organomegaly and lymphadenopathy. They were also examined sonographically for axillary and cervical lymphadenopathy. They also received a plain X-ray scan of the chest posteroanterior view. Eleven patients were screened by computerized tomography (CT) scan of the chest, abdomen, and pelvis. The choice of the imaging study depended on the affordability and availability of the imaging modality at the time of the patient's presentation. Two of our patients had a positron emission tomography (PET) scan; one of these two had been diagnosed with MF 17 years earlier. The other patient willingly asked for the PET scan. In all patients, imaging was not suggestive of any suspicious lymph node or internal organ involvement. None of the patients had a formal thyroid imaging prior to our study. TSH level averaged 2.2±3.71 lU/ml, total T3 was 1.09±0.20 ng/ml, and total T4 was 7.24±1.88. Twenty-six patients (92.9%) had a normal thyroid function test, and only two patients (7.1%) were biochemically hypothyroid. The level of anti-TPO antibody was 11.75±7.12 Ul/ml, which was positive in only two patients (7.1%). While 60.7% (17/28) of patients had normal thyroid echogenicity on ultrasound, 39.3% (11/28) of patients had hypoechogenic thyroid, which is suggestive of thyroiditis. A specific DTD-TIRADS algorithm has been used to detect the presence of features of diffuse thyroiditis. Eighteen patients (64.3%) had DTD-TIRADS I (normal thyroid), and 10 patients (35.7%) had DTD-TIRADS III and IV (diffuse thyroiditis). Regarding the thyroid gland size, 12 patients (42.9%) had a normal-sized thyroid gland, 15 patients (53.6%) had a small-sized thyroid gland, and only one patient (3.6%) had an enlarged thyroid gland. The mean volume of the right lobe was 5.46±2.61 ml, 3.71±1.5 ml for the left volume, and 3.90±0.49 ml for the isthmus. Regarding thyroid nodules, screening for thyroid nodules was done with risk stratification according to ACR-TIRADS 2017 [13]. Seventeen patients (60.7%) did not show any thyroid nodule. While 11 patients (39.3%) had thyroid nodules, five of these (45.5%) were not suspicious. i.e., TR1–2, and six of them (55.5%) were suspicious. i.e., TR3–4. None of the patients showed thyroid calcifications. The thyroid nodules were cystic in five patients, cystic with solid component in one patient, solid in four patients, and solid with cystic degeneration in another patient. As for the nodular echogenicity, it was anechoic in five patients and hypoechoic in six patients. There was no statistically significant correlation between the laboratory indication of thyroiditis (namely the anti-TPO) and the ultrasonic evidence of thyroiditis (the thyroid echogenicity) (*P*=0.147). There was a statistically significant relationship between the MF variant and DTD-TIRADS score

Table 1. Distribution of the studied MF patients (n=28) according to Type of MF and DTDTIRADS, Thyroid Nodules, Glandular Tissue Echogenicity, Thyroid Dysfunction, Anti-TPO, and TSH.

	MF Type						
	Hypopigmented		Patch		Poikilodermatous		
DTD TIRADS	N	%	N	%	N	%	Test of Significance
Category 1	1	20.0	10	62.5	7	100.0	X^2=8.182 P^{FE}=0.014*
Category 3 and 4	4	80.0	6	37.5	0	0.0	
Glandular tissue echogenicity							
Hypoechogenicity (thyroiditis)	4	80.0	7	43.8	0	0.0	X^2=8.138 p^{FE}=0.017*
Normal	1	20.0	9	56.3	7	100.0	
Nodules							
No	3	60.0	9	56.3	5	60.7	X^2=0.472 P^{FE}=0.866
Yes	2	40.0	7	43.8	2	39.3	
Thyroid dysfunction							
Normal	5	100.0	15	93.8	6	85.7	X^2=0.942 p^{FE}=0.685
Hypothyroidism	0	0.0	1	6.3	1	14.3	
Anti-TPO (Ul/ml)							
Negative	5	100.0	15	93.8	6	85.7	X^2=0.942 p^{FE}=0.685
Positive	0	0.0	1	6.3	1	14.3	
Mean ±SD	9.65±1.63		10.96±6.67		15.72±10.62		P=0.78 KW=5.106
Median	9.2		9.52		11.86		
Min-max	8.11-12.0		4.42-33.95		10.08-37.33		
TSH (ulU/ml)							
Mean ±SD	1.03±0.91		2.97±4.69		1.14±0.69		P=0.145 KW=3.864
Median	0.71		1.65		0.93		
Min-max	0.26-2.61		0.59-20.05		0.63-2.50		

x^2: Chi-squared test; *: *p*-value is significant at level <0.05; p^{MC}: Monte Carlo significance of Chi-squared test; p^{FE}: Fisher's Exact significance of Chi-squared test. *Abbreviations:* KW = Kruskal-Wallis test; MF = mycosis fungoides; TSH = thyroid stimulating hormone; TPO = thyroid peroxidase; SD = standard deviation.

(p^{FE}=0.014) (Table 1). Eighty percent of hypopigmented MF patients had features of thyroiditis (DTD-TIRADS III and IV) compared to only 37.5% of patients with classical patch stage. None of the patients with the poikilodermatous variant had features of thyroiditis. The same applied to the thyroid gland echogenicity, which was significantly related to MF variant (Table 1). Eighty percent of patients with hypopigmented MF had hypoechoic thyroid gland suggesting thyroiditis, compared to 43.8 % of patients with patch stage MF and to none of the patients with poikilodermatous MF (p^{FE}=0.017). Regarding the thyroid nodules (Table 1), they were found in 40% of hypopigmented MF patients, 43.8% of patients with patch stage, and 39.3% of patients with the poikilodermatous variant, with no significant difference. No statistically significant relationship was detected between different types of MF and the presence of hypothyroidism and anti-TPO antibody (Table 1). All hypopigmented MF patients had normal thyroid function and negative anti-TPO antibodies. Only one patient with the patch type was hypothyroid with positive anti-TPO antibodies, and only one patient with the poikilodermatous type was hypothyroid with positive anti-TPO antibodies. Patients treated with systemic PUVA were more likely to have thyroiditis (Table 2). All patients subjected to NBUVB had normal thyroid gland, compared to only 58.3% of patients undergoing systemic PUVA. However, this was not statistically significant (p^{FE}=0.265). Regarding thyroid nodules, 50% of NBUVB patients had thyroid nodules in comparison with systemic PUVA patients, of whom 39.3% had thyroid nodules. The mean duration of MF was a bit longer in patients with DTD-TIRADS III and IV (4.90±5.52 years) compared to patients with DTD-TIRADS I (4.56±4.42). However, this was not statistically significant. The same was true for thyroid nodules, where the duration of MF was 6.0±7.04 years in patients with thyroid nodules, compared to 3.82±2.24 years in patients without thyroid nodules.

Table 2. Distribution of the MF Patients (N=28) According to Treatment Modality, DTD TIRADS, and Thyroid Nodules.

	Treatment				
	NBUVB		Systemic PUVA		
DTD TIRADS	N	%	N	%	Test of Significance
Category 1	4	100.0	14	58.3	X^2=2.593 P^{FE}=0.265
Category 3 and 4	0	0.0	10	41.7	
Nodules					
No	2	50.0	15	62.5	X^2=0.225 P^{FE}=1.000
Yes	2	50.0	9	39.3	

x^2: Chi-squared test; *: *p*-value is significant at level <0.05; p^{FE}: Fisher's Exact significance of chi-squared test.

Conclusion

Mycosis fungoides is a rather indolent cutaneous T-cell lymphoma that may present in many variants. Similar to the study by Luo et al. [2], our hypopigmented MF patients were younger than patients with the other MF variants. In our study, patients with hypopigmented MF were significantly more likely to show hypoechoic thyroid gland suggesting thyroiditis (p^{FE}=0.017), with a statistically significant relationship between the MF variant and DTD-TIRADS score (p^{FE}=0.014). Eighty percent of hypopigmented MF patients had features of thyroiditis (DTD-TIRADS III and IV), compared to only 37.5% of patients with classical patch stage and to no patient with the poikilodermatous variant. The higher occurrence of sonographic thyroiditis in the hypopigmented variant may be attributed to the exaggerated recruitment of cytotoxic lymphocytes in this variant, manifested as predominance of epidermotropic CD8 lymphocytes, reported in 60–80% of patients [16,17].

The finding of higher DTD-TIRADS scores and higher occurrence of thyroid nodules in MF patients with longer duration of the disease, although without any statistical significance, may be related to the patients' aging. It is commonly reported that thyroid nodularity is more prevalent with advancing age [18,19].

Thyroid involvement in MF patients is an uncommon finding. However, in our study 39.3% (11/28) of patients had hypoechogenic thyroid, which is suggestive of thyroiditis, and 10 patients (35.7%) had DTD-TIRADS III and IV (indicating diffuse thyroiditis). Eleven patients (39.3%) had thyroid nodules. This form of thyroid involvement may be attributed to MF itself, where the thyroid gland may be affected by the lymphomatous process. Several studies support this notion. Burg [20] considered MF to behave as a systemic lymphoma from the start, hence any organ, including the thyroid gland, can be affected as a part of the extracutaneous dissemination. Some studies have reported thyroid nodularity in MF patients, such as the case report by Handa [21], and the report by Fuente et al. [9]. In the latter study [9], the biopsy of the thyroid nodules showed a granulomatous infiltrate with necrosis and atypical lymphocytes, which corresponded to the patient's granulomatous MF. In another case report, the biopsy finding of a thyroid nodule in an MF patient showed convoluted mononuclear cellular infiltrate suggestive of MF [22]. An old study in 1974 that analyzed the autopsies of MF patients found that the thyroid gland was infiltrated with MF cells in 14 out of 31 (42%) autopsies. The affected viscera usually have a characteristic cellular composition which closely resembles that of cutaneous lesions. These infiltrations might not be accompanied by destructive effects, thus preserving the thyroid function status [23].

MF patients may have a genetic predisposition and increased risk for developing Hashimoto's thyroiditis because both diseases are associated with an increased frequency of HLA-DR5 alleles [24]. Additionally, the association between MF and autoimmune disease may be due to underlying T-cell dysregulation, which is common in autoimmune diseases and MF [25].

Thyroid affection in MF patients as a second malignancy has been reported in a few studies. Hull et al. reported papillary thyroid carcinoma in association with MF in a 31-year-old male patient [26]. In another case report, a patient with Poland syndrome developed Sezary syndrome in addition to renal cell carcinoma and a third primary malignancy of the thyroid gland in the form a papillary thyroid carcinoma [27]. A rather old study reported thyroid carcinoma in association with MF, and both were successfully treated by radioactive iodine I-131 [28]. The exact explanation behind the association between MF and a second primary malignancy is still not clear, but possible mechanisms include the lymphomatous disorder itself, a genetic predisposition, other shared environmental predisposing factors, or the immunosuppressive therapy received for MF [26,27].

Central hypothyroidism is a very common, dose-dependent, reversable side effect of the synthetic selective

X receptor retinoid bexarotene, which is used to treat MF [29]. Central hypothyroidism with bexarotene, reported in 85% to 100% of patients, necessitates thyroid hormone replacement therapy [30]. Bexarotene is suggested to have two fundamental effects on thyroid function: suppressing TSH production and increasing thyroid hormone metabolic clearance [31].

Denileukin diftitox, a recombinant fusion protein of diphtheria toxin and the ligand-binding domain of human IL-2, causes transient thyrotoxicosis shortly after initiating treatment for MF, which may lead to permanent hypothyroidism. The exact etiology of this thyroiditis is unknown, but it may be attributed to cytokine-mediated thyroid injury or immune dysregulation [32].

Our institute follows the recommendations of the United States Cutaneous Lymphoma Consortium as regards the treatment of early-stage MF with phototherapy, either PUVA or NB-UVB, which has proved to be both safe and effective [33]. In our study, none of the patients receiving NB-UVB phototherapy had sonographic evidence of thyroiditis, compared to 41.7 % of patients receiving systemic PUVA, who had DTD-TIRADS III and IV. Prolonged exposure to phototherapy, especially PUVA, carries a potential risk of cutaneous malignancies in psoriatic patients [34]. The thyroid gland has a rather superficial unprotected location under the skin. Nevertheless, another study on psoriatic patients failed to demonstrate any influence of PUVA on the thyroid hormones [35]. Limited data are available as regards the possible carcinogenic effects of phototherapy in MF patients. In a recent study by Dogan et al. [36], of a total 104 MF patients, 15.4% developed cutaneous malignancies and only eight developed internal malignancies in the form of solid organ tumors or lymphomas. The main contributing factor to the development of malignancy was the total number of PUVA sessions (<250 vs ≥250 sessions). Additional factors that may also increase the possibility of a second malignancy in MF patients include an inherent biological predisposition and environmental chemical predisposing factors [37].

Thyroid affection in MF patients is somewhat different when compared to the general population. The prevalence of positive anti-TPO antibodies in adults varies significantly across different countries. This may be related to different ethnic populations, environmental factors, socioeconomic status, and/or dietary habits. In the present study, the level of anti-TPO antibody was 11.75±7.12 IU/ml and was positive in only two patients (7.1%). This percentage is lower than that in the general population, as described in several studies such as in the meta-analysis by Hu et al. (7.8%) [38] and the study by Amouzegar et al. (12.8%) [39]. In the current study, 35.7% of MF patients had ultrasound evidence of thyroiditis with DTD-TIRADS III and IV. This percentage (35.7%) is much higher than that present in the general population according to Hu et al. (13.2%) [38] and also higher than that in the study by Assaad et al. (9%) [40], which was carried out in the same geographical region as our study. Hence, we can conclude that the prevalence of thyroiditis by ultrasonographic features is greater in patients with MF in comparison to the general population. Regarding thyroid nodules, 39.3% of this study's patients had thyroid nodules. This was higher than in the study by Asaaad et al. (17.5%) [40], which was carried out in the same geographical population as our study; the incidence of thyroid nodules in our MF patients was also higher than that in the study by Mu et al. (24.83%) [41].

The limitations of the current study include single center-acquired data, the lack of controls, a small number of patients, and the lack of histological confirmation of thyroid gland affection.

Mycosis fungoides can be associated with sonographic evidence of thyroiditis and thyroid nodules, especially in patients with the hypopigmented variant, those receiving systemic PUVA, and those with prolonged duration of the disease. In the literature, thyroid affection in MF has been reported as part of the disease spectrum, as a second malignancy, or as a drug side effect. Hence, we recommend regular screening for thyroid gland affection in all MF patients.

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