Electronic Journal of General Medicine
2022, 19(6), em409
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Original Article

OPEN ACCESS

Autoimmune thyroiditis associated with autoimmune diseases

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Citation: Ben Salah R, Hadj Kacem F, Soomauro S, Chouaib S, Frikha F, Charfi N, Abid M, Bahloul Z. Autoimmune thyroiditis associated with autoimmune diseases. Electron J Gen Med. 2022;19(6):em409. https://doi.org/10.29333/ejgm/12399

ARTICLE INFO

Received: 17 Mar. 2022

Accepted: 5 Aug. 2022

ABSTRACT

Introduction: Autoimmune thyroid disorders are frequent. Patients diagnosed with these autoimmune thyroid diseases (AITD) are at high risk of developing other autoimmune diseases (AD), which at times, can be fatal.

Aim: The aim of this study is to identify epidemiological, clinical, and biological characteristics of the different associations of organ-specific AD and non-organ-specific AD or systemic diseases with AITD and compare our findings with that found in literature.

Patients and methods: It is a descriptive retrospective single institution study. We collected data from 113 patients diagnosed with a thyroid disorder associated with an autoimmune disease-either organ-specific autoimmune disease or systemic disease- hospitalized over a period of 18 years.

Results: The sex ratio (F/M) was 3.52. The median age of occurrence of the AITD was 38.22 years' old. The aetiology of the AITD was mainly Hashimoto's disease in 69 patients followed by Grave's disease in 19 patients. Seventeen types of AD were identified in association with the AITD. The most frequent organ-specific AD associated with the thyroid disorder was type 1 diabetes mellitus (41 patients), vitiligo (16 patients) and pernicious anaemia (16 patients). Systemic lupus erythematous (12 cases) and Sjogren's disease (12 cases) were the most common systemic diseases associated with the AITD.

Conclusion: AITD are frequent and can be associated with one or more autoimmune diseases. These AD can sometimes be revealing or on the contrary can emerge years later after the diagnosis of the dysthyroidism. A long-term follow-up is warranted in all patients diagnosed with an autoimmune disease.

Keywords: autoimmune thyroiditis, systemic diseases, autoimmune diseases

INTRODUCTION

Autoimmune thyroid diseases (AITD) result from a dysregulation of the immune system leading to an immune attack on the thyroid [1]. AITD are T cell-mediated organ-specific autoimmune disorders characterized by the presence of a lymphocytic infiltration of the thyroid gland and the presence of high titers of anti-thyroid antibodies (ATA) in a genetically predisposed person [1].

AITD are the most frequent autoimmune disorders, and their prevalence is estimated around 5% [1]. AITD can be associated with other AD, they may be organ-specific AD or systemic AD. These affiliations are not infrequent [2]. They can be clustered together forming the autoimmune polyendocrine syndrome or multiple autoimmune syndromes. This study highlights the characteristics of AD associated with AITD.

PATIENTS AND METHODS

It is a descriptive retrospective single institution study that collected data from patients diagnosed with a AITD associated with an AD-either organ-specific AD or systemic disease- hospitalized in the endocrinology and the internal medicine units at the Hedi Chaker University Hospital, Sfax over a period of 18 years (as from January 2000 to December 2017). The study was carried out in accordance with the Declaration of Helsinki. This study was a non-interventional study with no addition to standard care. All data were obtained only for standard diagnostic following physicians' prescriptions (no specific sampling, no modification of the sampling protocol). All patients from our institution are informed that their clinical data can be used for research and give their consent for the use of their data unless they provide an opposition to it. Data analysis was carried out using an anonymized database. The inclusion criterion was any patient with an AITD associated with another AD. The diagnosis of the AITD was established from the clinical presentation, thyroid hormones (TSH levels and free T4 levels) and thyroid autoantibodies (thyroid peroxidase antibodies (TPO Ab), thyroglobulin antibodies (Tg Ab) and thyroid-stimulating-hormone receptor antibodies (TRAb), positivity was set at >70UI/L, >100UI/L, and >2UI/L, respectively) measurements. The aetiology for hypothyroidism were mainly the chronic lymphocytic Hashimoto's thyroiditis - defined by the presence of a high titer of the ATA (TPO Ab

Table 1. Autoimmune thyroid disease and autoimmune diseases

	Autoimmune disease	Number of patients	Frequency (%)
Organ-specific autoimmune diseases	Type 1 diabetes	41	31.53
	Adrenocortical insufficiency	7	5.38
	Pernicious anemia	16	12.31
	Coeliac disease	5	3.85
	Auto immune hepatitis	1	0.77
	Myasthenia	1	0.77
	Vitiligo	16	12.31
	Lichen planus	1	0.77
	Alopecia areata	2	1.54
	Bullous pemphigoid	1	0.77
Non-organ-specific autoimmune diseases	Systemic lupus erythematous	12	9.23
	Sjögren's disease	12	9.23
	Systemic scleroderma	2	1.54
	Rheumatoid arthritis	9	6.92
	Mixed connective tissue disease	1	0.77
	Antineutrophil cytoplasmic antibody positive vasculitis	2	1.54
	Antiphospholipid syndrome	1	0.77

and/or Tg Ab) and the presence of a goiter, and the chronic lymphocytic atrophic thyroiditis defined by the onset at a later age, the presence of an atrophic thyroid gland documented by thyroid ultrasound and the positivity of serum thyroid antibodies. The main aetiology for hyperthyroidism was Graves' disease (GD) defined by the pathognomic association of thyrotoxicosis, a goiter and an exophthalmos combined with TRAb positivity. Another aetiology was hashitoxicosis defined as the hyperthyroid phase of Hashimoto's thyroiditis. The autoimmune thyropathy in euthyroid phase was characterized by the positivity of ATA but with normal thyroid function. The diagnosis of type 1 diabetes mellitus (T1DM) was established using the American Diabetes Association (ADA) diagnostic criteria [3]. The diagnosis of adrenal insufficiency was based on serum cortisol levels <50ng/ml or <200ng/ml after the synacthen test along with a high serum level of adrenocorticotrophic hormone (ACTH). The positivity of the adrenal antibodies was necessary to affirm the autoimmunity.

The American College of Rheumatology (ACR) classification criteria for systemic lupus erythematous (SLE) of 1982 revised in 1997 [4] and the American European Consensus Group (AECG) diagnostic criteria [5] were adopted for diagnosing SLE and Sjogren's disease, respectively. Similarly, the ACR/European League against rheumatism 2010 (ACR/ EULAR) [6] was used for the diagnosis rheumatoid arthritis (RA).

Antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis identified in our study was drug-induced and the diagnosis was established using the ACR diagnostic criteria [7]. In some cases, there may be more than two AD associated in the same individual. In our study, we investigated the presence of multiple autoimmune syndrome (MAS). It is defined as the combined occurrence of at least three AD in the same person [8]. In each patient, we also investigated the existence of autoimmune polyendocrine syndromes (APS) which are uncommon constellations of organ-specific AD characterized by the occurrence of more than one endocrine AD in an affected individual [9,10].

Statistical analysis was performed using SPSS software (version 20). The Chi-square test was used to compare qualitative variables or frequencies and the student test for the comparison of quantitative variables. A p-value ≤0.05 was considered statistically significant.

RESULTS

Our study counted 113 patients diagnosed with an AITD.

Among the 113 patients studied, 77.88 % were female (F/M=3.52). The median age of patients was 48.76 years' old. Twenty- patients reported family history of dysthyroidism.

The onset of the thyroiditis was predominantly high in the age group of 31 to 40 years old in both sexes. The five different types of thyroiditis found in our study was overt hypothyroidism in 67 patients (59.3%), overt hyperthyroidism in 29 patients (25.7%), subclinical hypothyroidism in six patients (5.3%), subclinical hyperthyroidism in two patients (1.7%) and auto immune thyropathy in nine patients (8%).The circumstances that led to the discovery of the thyroiditis were clinical manifestations in 48.7%, coincidental in 36.3%, due to a complication in 1.8%.The chronic lymphocytic Hashimoto's thyroiditis was diagnosed in 69 patients (61%) including 10 men and 59 women. The median age at discovery was 37.8 years old. The TPO Ab were positive in 62 patients and Tg Ab were positive in 41 patients. We counted four cases (3.54%) of chronic lymphocytic atrophic thyroiditis.

The most common cause of hyperthyroidism was grave's disease, diagnosed in 19 patients (16.8%), including 10 men and 9 women. The median age of disclosure of the disease was 35.52 years old. The TRAb were positive in all patients as well. Hashitoxicosis was diagnosed in 12 patients (10.6%), consisting of 10 women and two men. The median age upon occurrence of the disease was 36.83 years old. The Tg Ab and TPO Ab were positive in all patients.

In our study, 17 types of AD were found in patients with AITD, which consisted of 10 organ-specific AD and seven systemic diseases. 95 patients (84.1%) had another AD associated with the AITD, 17 patients (15%) had two AD and only one patient had three AD other than that of the thyroiditis. The different associations are detailed in **Table 1**.

In each patient with AITD, one or more AD was identified and thus we found 11 cases of MAS and 46 cases of APS shown in **Table 2** and **Table 3**.

Table 2. Different types of multiple autoimmune syndrome

Type of MAS	Type of AITD	AD associated		Number of patients
MAS type 2	Hypothyroidism	Rheumatoid arthritis + Sjogren's syndrome		2
MAS type 3	Hypothyroidism	T1DM	+ Vitiligo	2
			+ Vitiligo + pernicious anemia	1
			+ Adrenocortical insufficiency	2
			+ SLE	1
		Sjogren's disease	+ Pernicious anemia	1
			+ Vitiligo	1
		Systemic lupus erythematous + pernicious anemia		1

Note. MAS: Multiple autoimmune syndrome; AITD: Autoimmune thyroid disorder; SLE: Systemic lupus erythematosus; & T1DM: Type 1 diabetes mellitus

Table 3. Different types of autoimmune polyendocrine syndrome

Type of APS	Type of AITD	AD associated	Number of patients
APS type 2	Hypothyroidism	Adrenocortical insufficiency	4
		Adrenocortical insufficiency + T1DM	2
	Hyperthyroidism	Adrenocortical insufficiency	1
APS type 3	Hyperthyroidism	T1DM	15
	Hypothyroidism		17
	Autoimmune thyropathy in euthyroid phase		7

Note. APS: Autoimmune polyendocrine syndrome/autoimmune polyglandular syndrome; AITD: Autoimmune thyroid disorder; AD: Autoimmune disease; & T1DM: Type 1 diabetes mellitus

In this series, the AITD was diagnosed, before the occurrence of the AD in 35 cases (26.51%), after the occurrence of the AD in 54 cases (40.92%) and concomitant to the diagnosis of the AD in 40 cases (30.3%).

T1DM was found to be the most commonly associated with AITD. It was diagnosed in 41 patients (31.53%) which consisted of 25 women and 16 men. The median age upon discovery of the T1DM was 30.49 years' old. It was associated with an overt hypothyroidism in 19 patients, an autoimmune thyropathy in euthyroid phase in 7 patients, an overt hyperthyroidism in 15 patients. The T1DM preceded the diagnosis of the thyroid disorder in 24 cases with a median period of 69 months and succeeded the latter in six cases within a mean period of 40 months. In 11 cases, both diagnoses were concomitant.

An Adrenal insufficiency was diagnosed in seven patients (5.38%) in which six female and one male. The median age of revelation was 35.14 years' old. It was confirmed by a low serum cortisol level with a median of 38.88 ng/ml. The synacthen test was indicated in two patients. The mean serum cortisol level at T60 was 24.3 ng/ml. The primary origin of the adrenal insufficiency was attested by a mean serum hormone ACTH level of 1,510.9 ng/l. The anti-adrenal antibodies were positive in all patients thus affirmative of the autoimmune origin. This organ-specific AD was associated with hypothyroidism in six patients and hyperthyroidism in one patient. In this study, we counted five cases of Schmidt syndrome, which is characterized by the association of autoimmune adrenalitis (Addison's disease) and AITD.

Pernicious anaemia (PA) was associated with AITD in 16 patients (12.31%), which included 13 women and three men. The former predated the AITD in seven patients by a mean period of 50 months.

Other organ-specific AD associated to AITD found in our study was coeliac disease (five cases), autoimmune hepatitis (one case) and myasthenia (one case).

Dermatologic AD included vitiligo found in 16 cases, alopecia areata found in two cases and lichen planus just as bullous pemphigoid found in one case each.

Autoimmune thyroid disorder was associated with a non-organ-specific AD in 39 cases. The most frequent systemic diseases were SLE, Sjogren's disease and RA.

SLE was diagnosed in 12 female patients (9.23%). The median age upon discovery of the SLE was 31.17 years old. SLE was associated with hypothyroidism in 10 patients, autoimmune thyropathy in euthyroid phase in one patient and hyperthyroidism in one patient. The AITD was diagnosed prior to the SLE in five cases with a mean period of 38.8 months. Both diagnoses were concomitant in seven remaining cases. The Sjogren's syndrome (SS) was also diagnosed in 12 of our patients (9.23%). All of them were women. The median age of revelation was 50.33 years old. It was affiliated with hypothyroidism in 10 patients and hyperthyroidism in two patients. The diagnosis of the SS succeeded that of the thyroid disorder in six patients with a mean period of 52 months and both diagnoses were concomitant in the other six patients.

The subjective dry mouth symptom was reported in all patients whereas the ophthalmology tests confirmed the xeropthalmia in 10 patients. The ANA were positive in 10 patients (anti-SSA in eight patients and anti-SSB in three patients). In our study, nine patients (6.92%) were diagnosed with RA associated with AITD, consisting of six cases of hypothyroidism, two cases of hyperthyroidism and one case of autoimmune thyropathy in euthyroid phase. The median age of revelation of this systemic disease was 44.25 years old. The immunologic tests done showed a positivity of the rheumatoid factor in five patients, autoantibodies against cyclic citrullinated peptides (anti-CCP) were positive in three patients.

We came across two cases (1.54%) of ANCA-associated vasculitis linked to the treatment of GD. Both patients were treated with benzyl-thiouracil. After a mean period of 20 months, they developed systemic symptoms (fever, polyarthritis, and skin lesions). A panel of test was done showing ANCA positivity, specifically anti-myeloperoxidase antibodies. They were ultimately diagnosed with drug-induced (benzyl-thiouracil) ANCA vasculitis. The treatment was

promptly discontinued, and patients were treated by corticosteroid courses.

Other systemic diseases discovered in our study were systemic scleroderma in two cases (1.54%), mixed connective tissue disease in one case (0.77%) and the anti-phospholipid syndrome was equally found in one case (0.77%).

DISCUSSION

In our study, we have quantified the different AD associated in patients diagnosed with AITD. AITD are the most prevalent organ-specific AD and constitute a serious public health problem. They are frequently associated with other AD [11].

113 cases of AITD were associated with an organ-specific AD (70%) and systemic diseases (30%). The most common AITD in association with another AD was Hashimoto's disease (61.1%). Graves' disease (GD) was associated with another AD in 16.8%. Thus, Hashimoto's disease was more frequently associated compared to GD and our results were similar to that found in literature. In [12], the athors provide strong evidence of significantly increased risks of coexisting AD in subjects with AITD: some 9.67% of 2,791 subjects with GD and 14.3% of 495 patients with Hashimoto's thyroiditis had another AD.

Women represented 77.9% of our population (F/M=3.52). Our results were in accordance with that found in literature where a clear female predominance was identified with a sex ratio (F/M) varying from 5 to 20 [13]. In our study, this female preponderance was evidently found in patients with Hashimoto's disease (F/M=5.26) compared to that found in patients with GD (F/M=0.9).

The median age upon discovery of the AITD was 38.22 years' old. The median age of occurrence of the AITD in our study is indeed in compliance with data found in literature.

The different AD can be organized into MAS and APS.

The MAS was described by Humbert and Dupond in 1988 [14]. There are a number of factors implicated in the development of MAS including familial, genetic and epigenetics, infectious, immunological, and psychological factors [14]. In [15], it was concluded that AITD was the most common and recurrent pathology found in MAS. In our study, we counted two cases of MAS type-2 and nine cases of MAS type-3.

Besides MAS, another well-known example of poly-autoimmunity is the APS. The loss of immunological tolerance to self-antigens may afflict multiple organs systems thus generating in the same patient the APS [16]. They are of four types. The AITD is one of the pillars of these syndromes essentially in the APS type 2 and 3. The former was the most frequent APS (80%) also known as the Schmidt's syndrome defined by the presence of these two elements: Addison's disease (100%) and AITD (69-82%) [17]. In our study, we found 46 cases of APS divided into seven cases of APS type-2 and 39 cases of APS type-3. Data found in literature highlights the fact that APS are frequent in patients with AITD and thus the hunt for other autoimmune endocrine diseases is imperative in these patients.

The AITD is the most widespread among patients with T1DM [18]. Their prevalence is two to three times higher in the T1DM population than that of the general population. As a matter of fact, 6.6% out of 10% of healthy adults have positive ATA compared to 20% out of 40% of the type 1 diabetic adults [19]. According to [20], the T1DM is associated with Hashimoto's disease in 14-28% of cases. In other studies, T1DM is associated to GD in only 0.5-7% of cases [21-22].

The T1DM was the most common AD associated with AITD in our study. It was affiliated with Hashimoto's disease in 26 cases (63.4% of cases) and with GD in 15 cases (36.6% of cases). Several studies demonstrated that AITD was more frequent in diabetic women than in men [21]. Our findings match that of literature as we noted a clear predominance of type 1 diabetic women.

The ADA recommend serum TSH assay upon discovery of diabetes in patients bearing hypothyroid or hyperthyroid symptoms, then every one to two years as follow up [22].

In our study, we identified seven cases of autoimmune adrenal insufficiency (5.38% of the association AD and AITD).

Adrenal insufficiency is a rare life-threatening disorder, first described in 1855 [23]. Auto immune adrenalitis is the first cause of primary adrenal insufficiency. Antibodies against steroid 21-hydroxylase are detected in about 85-90% of cases. It may be isolated or part of the APS (60%) type 1, 2, and 4 [24].

In a multicenter study of 3,286 patients diagnosed with AITD, the prevalence of Addison's disease in patients with GD and in patients with Hashimoto's disease was 0.13% and 4.11% respectively [12]. In fact, the risk of acute adrenal insufficiency is 2.5 times higher in patients with Addison's disease in the context of APS type 2 [25].

Other AD associated with AITD was retrieved in our study. Biermer's disease was found in 16 patients and coeliac disease in five patients representing 12.31% and 3.85% of the association of AD and AITD, respectively.

The association between autoimmune atrophic gastritis and thyroid disorders has been observed since the early 1960 and the expression "thyro-gastric syndrome" was used to indicate the presence of ATA or AITD in patients with PA [26]. From a clinical point of view, the thyro-entero-gastric autoimmunity may lead to potentially serious consequences like anemia, micronutrients deficiencies, and drugs malabsorption [27]-problems may arise in the substitution of L-thyroxin in these patients-as well as to an increased risk for the development of gastric, thyroidal, and intestinal malignancies [28]. Thus, it is necessary to screen and dig for these AD in patients with AITD to prevent diagnosis and treatment delays.

Seven types of systemic diseases were identified in our series namely systemic lupus erythematous (SLE, n=12), Sjogren's disease (SS, n=12), rheumatoid arthritis (RA, n=9), systemic scleroderma (n=2), mixed connective tissue disease (n=1), ANCA-associated vasculitis (n=2) and the anti-phospholipid syndrome (n=1).

SLE was found in 12 cases, representing 9.23 % of the association AD and AITD. It is more predominant in women aging from 20 to 30 years [29]. Multiples studies claim the fact that thyroiditis is the most frequent AD in case of SLE [29]. There are emerging theories and evidence suggesting a genetic predisposition for the association between SLE and thyroiditis. Patients carrying a particular R620W polymorphism in the PTPN22 gene encoding a T-cell protein are more likely to develop concurrent SLE and thyroid disease and not SLE alone [30].

The prevalence of AITD in patients with SLE was 90-fold (Hashimoto's disease) and 68-fold (Grave's disease) than that

Table 4. The frequency of association of AITD and AD in our study comparatively with other studies (No & F)

Autoimmune diseases associated	Study 1 [39] n=3,069 AITD	Study 2 [12] n= 3,286 AITD	Study 3 [31] n= 426 AITD	Our study n= 113 AITD
T1DM	31 (1.01%)	36 (1.1%)	7 (1.64%)	41 (31.53%)
Addison's disease	7 (0.22%)	10 (0.3%)	4 (0.94%)	7 (5.38%)
Pernicious anemia	87 (2.83%)	58 (1.77%)	5 (1.17%)	16 (12.31%)
Celiac disease	39 (1.27%)	30 (0.9%)	0	5 (3.85%)
Vitiligo	83 (2.7%)	53 (1.61%)	6 (1.41%)	16 (12.31%)
Alopecia	16 (0.52%)	0	0	2 (1.54%)
Autoimmune hepatitis	0	0	0	1 (0.77%)
Lichen planus	0	0	0	1 (0.77%)
Bullous pemphgoid	0	0	0	1 (0.77%)
Myasthenia gravis	3 (0.1%)	7 (0.2%)	2 (0.47%)	1 (0.77%)
Rheumatoid arthritis	74 (2.41%)	109 (3.3%)	9 (2.11%)	9 (6.92%)
Systemic scleroderma	16 (0.52%)	12 (0.37%)	9 (2.11%)	2 (1.54%)
Sjogren's disease	27 (0.87%)	0	40 (9.4%)	12 (9.23%)
SLE	25 (0.81%)	18 (0.55%)	25 (5.9%)	12 (9.23%)
MCTD	0	0	38 (8.9%)	1 (0.77%)
ANCA-positive vasculitis	0	0	0	2 (1.54%)
Antiphospholipid syndrome	0	0	0	1 (0.77%)

Note. AITD: Autoimmune thyroid disease; T1DM: Type 1 diabetes mellitus; SLE: Systemic lupus erythematous; MCTD: Mixed connective tissue disease; ANCA-positive vasculitis: Antineutrophil cytoplasmic antibody positive vasculitis; No: Number of patients; & F: Frequency of association

of the general population [31]. Numerous studies confirm that a relatively high number of patients with SLE (20-45%) have ATA, compared to 10% in the general population [32].

In our study, we noted 12 cases of AITD associated with SLE, mainly Hashimoto's disease in 10 cases (83.3 %). Sjogren syndrom is probably the most frequent systemic disease associated with AITD. There is a clear preponderance in women (F/M=9/1) [33]. In our study, all patients were female.

The strong association of between SS and AITD suggests a common pathogenic mechanism in both diseases. The participation of HLA of the haplotypes HLA-B8 and DR3 in both SS and AITD is demonstrated by the higher frequency of those haplotypes in Caucasian patients with these diseases [34]. According to Lazurova and Benhatchi, the prevalence of AITD particularly hypothyroidism is 10-fold in patients diagnosed with SS than the general population [35]. In our study, SS was associated with hypothyroidism in 10 cases and in two cases with hyperthyroidism.

RA is the most frequent chronic inflammatory rheumatism. In this series, nine patients presented RA associated with AITD. Studies have shown a major predominance of AITD in patients with RA and vice versa. In fact, the prevalence of RA in patients with AITD is 1 to 3-fold and the prevalence of AITD in patients with RA is 1 to 6-fold [36]. Chen et al made clear that the presence of ATA was associated with joint destruction in patients with RA, suggestive of the detrimental effect of these thyroid antibodies on the joint [37,38]. Interestingly, the use of methotrexate reduced the ATA titers specifically TPO Ab [39]. Thus, demonstrating the importance of screening and monitoring of thyroid function in patients with RA.

The different association of AITD and AD in our study comparatively with other studies shown in **Table 4**.

Our study suggests that there are common pathogenic mechanisms–physio pathological mechanisms, genetic predisposition, and risk factors- for developing AD called the autoimmune tautology [40]. The clinical evidence of the latter highlights the co-occurrence of more than one AD in a single patient giving rise to a form of poly-autoimmunity, the APS and/or the MAS [16]. The importance of defining these terms is due to the fact that patients with poly-autoimmunity may have a modified disease course (a worse prognosis or a better one) and a modified clinical presentation [40].

Genetics play a key role in the pathogenesis of AITD. In fact, a number of immune-related genes have been implicated in genetic susceptibility to AITDand these genes may be common for other AD. A genetic study in these patients would be the key to explain all these complex genetic mechanisms implicated in the onset of AD so as to effectively screen these patients and prevent complications linked to these associations.

Our study acknowledged fields that needed improvement: the insufficient screening of AD in family members of patients diagnosed with an AD and the limited number of patients compared to other studies.

The major positive point of our series is that we studied all associations of organ-specific AD as well as systemic diseases in patients with AITD. It is of great importance to highlight the fact that our study is the first of its kind in Tunisia and Africa. There are no other similar studies.

In conclusion, patients with AD must be considered at risk for other AD particularly AITD. Hence, we propose a regular screening and monitoring of the thyroid function by meticulous clinical examination and laboratory tests (serum TSH levels and ATA assays) must be systematically done in any suspicion of thyroid dysfunction.

In the same spectrum, a patient with AITD must be regularly monitored for the early screening of other AD. A long-term follow-up seems necessary.

Our study confirms the high prevalence of AD in patients diagnosed with AITD. Surely, there is a common autoimmune pathogenic mechanism in a genetically predisposed terrain, but our study does not permit us to conclude on this point. Other studies are essential including genetic studies in order to discern patients at risk for developing autoimmune diseases.

Author contributions: RBS & FHK: conceived the idea, developed the study design; **SS:** wrote the manuscript; **SC:** analyzed the data; **FF & NC:** collected data; **MA & ZB:** drafted the manuscript; & **all authors:** analyzed data and edited the article. All authors have agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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