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ORIGINAL ARTICLE

Rheumatic manifestations of euthyroid, anti-thyroid antibody-positive patients

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Abstract The aim of this study is to define the rheumatic manifestations of euthyroid patients with chronic lymphocytic thyroiditis (CLT) but without a well-defined connective tissue disease. Forty-six consecutive patients with anti-thyroid peroxidase (αTPO) and/or anti-thyroglobulin antibodies (αTG), and normal thyroid function in the absence of a well-defined connective tissue disease were included in a case–cohort study. Arthralgias were a presenting complaint in 98 % of patients. Fibromyalgia syndrome was found in 59 % of patients. Raynaud's phenomenon occurred in 28 % and sicca symptoms in 26 % of patients. Two patients had seronegative arthritis resembling rheumatoid arthritis. Arthritis was radiographically present in 88 %, affecting the spine in 45 % of patients. Thyroid-stimulating hormone (TSH) levels positively correlated with levels of αTPO, but not with erythrocyte sedimentation rate (ESR) or αTG levels. A positive ANA was found in 24 % of patients. One patient developed subclinical hypothyroidism during the study. Rheumatic manifestations frequently occur in patients with CLT in the absence of overt thyroid dysfunction and mimic the presentation of the well-defined connective tissue diseases.

Keywords Autoimmune thyroid disease · Chronic lymphocytic thyroiditis · Hashimoto thyroiditis · Fibromyalgia · Arthritis

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Introduction

Autoimmune thyroid disease (AITD) refers to a spectrum of disease that includes Grave's thyroiditis and chronic lymphocytic thyroiditis (CLT), also known as Hashimoto thyroiditis. The hallmark of AITD is lymphocytic infiltration of the thyroid gland, a process much more marked in CLT than in Grave's disease [1]. As a consequence of the immune reaction in CLT, thyroid cells appear enlarged with a distinct granular and pink cytoplasm known as Hürthle or Askanazy cells [2]. Diagnosis of CLT can be made on the basis of the presence of anti-thyroid antibodies including anti-thyroid peroxidase (αTPO) and anti-thyroglobulin (αTG) antibodies, found in 20–50 and 90–95 % of patients, respectively [3], ultrasonographic evidence of hypoechogenicity and heterogeneity of the thyroid gland [4], a palpable goiter frequently with an uneven surface to palpation, and histological evidence of thyroiditis [5]. The sustained presence of anti-thyroid autoantibodies alone probably supports the presence of some degree of autoimmune thyroiditis even in the absence of the other confirmatory findings and is sufficient to make the diagnosis [2, 6]. The prevalence of anti-thyroid autoantibodies in the US population without overt thyroid disease has been estimated to be about 11 % [7].

Clinically, AITD manifests as hyperthyroidism in association with Grave's disease or as hypothyroidism as a consequence of CLT [1]. Rheumatic signs and symptoms have been described in association with AITD [2, 8]. The range of arthritis presentations associated with CLT in particular have been reviewed elsewhere and include osteoarthritis, inflammatory osteoarthritis, seronegative inflammatory arthritis and arthritis associated with well-defined connective tissue disease (WDCTD) [9]. Briefly, osteoarthritis has been described in association with

clinical hypothyroidism, presenting with non-inflammatory joint effusions [10]. Seronegative arthritis resembling rheumatoid arthritis has been documented in CLT patients who are not necessarily hypothyroid [11]. Its association with other WDCTDs has also been shown, with Sjogren's syndrome, rheumatoid arthritis and systemic lupus erythematosus being commonly associated WDCTDs [12, 13]. Lastly, it is becoming increasingly apparent in both the endocrinology and rheumatology literature that there is a significant association between CLT and chronic widespread pain syndromes including fibromyalgia [13, 14].

Since there were no studies describing fully the rheumatic manifestations of the subset of patients with CLT who have normal thyroid function, the present study was conceived as a preliminary effort to define the clinical presentation of euthyroid, CLT patients referred to a rheumatology practice with rheumatic complaints but without a WDCTD or other primary rheumatic diagnoses to explain their findings. The study also asked whether CLT was associated with undifferentiated connective tissue disease (UCTD).

Methods

For a 6-year period between January 2006 and December 2011, all referrals to a rheumatology practice (CET) without a clearly diagnosed rheumatic disease were screened for anti-thyroid autoantibodies as anti-thyroid peroxidase (αTPO) or anti-thyroglobulin (αTG) antibodies. Study design was a retrospective cohort study including 46 consecutive patients who tested positive for αTPO and/or αTG. Positive values for the anti-thyroid autoantibodies *αTPO* and *αTG* were >5 and >10 IU/mL, respectively. Laboratory values at the time of initial evaluation were analyzed for this study as were radiographs. Body mass index (BMI) was from the initial visit. All data, acquired as part of usual care, were analyzed retrospectively.

The presence of osteoarthritis and other WDCTD was ascertained using American College of Rheumatology (ACR) classification criteria [15]. The 1987 classification criteria for rheumatoid arthritis and the 1997 criteria for systemic lupus erythematosus (SLE) were used [16, 17]. Application of the 2010 ACR/European League Against Rheumatism classification criteria post hoc did not affect the composition of the study cohort [18]. Fibromyalgia was also diagnosed based on ACR criteria [19]. Classification criteria for UCTD were from Mosca et al. [20]. Severity of fibromyalgia was scored on a Likert-type scale with none = 0, mild = 1, moderate = 2 and severe = 3. Morning stiffness was similarly scored none = 0, minimal or mild = 1, moderate = 2 and severe = 3.

Inclusion criteria

Subjects were included in the study if they had αTPO and/or αTG positivity with or without ultrasonographic or histological evidence of CLT. TSH had to be within normal limits (0.4–4.6 μU/mL) at the time of referral to rheumatology for inclusion in the study. Generalized body pain and joint pain were the main reasons for referral to rheumatology.

Exclusion criteria

Having a well-defined rheumatic disease including gout, pseudogout, WDCTD including rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease (MCTD), systemic sclerosis, inflammatory myositis (dermatomyositis, polymyositis or inclusion body myositis), chronic active hepatitis C, human immunodeficiency virus (HIV) with uncontrolled viremia, post-infectious arthritis, seronegative spondyloarthritis, psoriatic arthritis, hypothyroidism or subclinical hypothyroidism with TSH at the time of referral between the upper limit of normal in our laboratory of >4.6 and 10 μU/mL were considered exclusion criteria for the study.

Statistics

Descriptive statistical analyses were performed using the mean, range and standard deviation of variables. Correlations of statistical significance between groups were carried out using Spearman's rank correlation. P values <0.05 were considered to be significant.

Ethics

The study was approved by the institutional review board of the Albert Einstein College of Medicine, New York.

Results

Demographic and basic laboratory data

The mean age of this study group was 49.1 years. All 46 subjects except 1 were female. The cohort had a mean BMI of 29.5 (Table 1). The mean erythrocyte sedimentation rate (ESR) was 19.0 mm/h. Twelve (27.3 %) subjects had ESRs exceeding 20 mmHg. The mean C reactive protein (CRP) was 0.49 mg/dL. Seven (15.9 %) individuals had greater than the normal value of CRP of <0.9 mg/dL, with most subjects showing a non-inflammatory pattern of acute-phase reactants (APRs). Serum immunoglobulins were similarly close to normal range (Table 1). The most likely

Table 1 Demographic and laboratory characteristics of study cohort

	Mean, *n*	Range	Standard deviation
Age (year)	49.1, 46	23–79	11.45
Sex, 45 F, 1 M			
BMI	29.47, 46	15.8–42	5.69
ESR (mm/h)	18.95, 44	2–65	14.99
CRP (mg/dL)	0.49, 43	0.1–1.3	0.38
Igs (mg/dL)			
IgG	1,431.5, 43	985–2,260	282.84
IgM	131.88, 43	50–278	73.18
TSH (μU/mL)	1.99, 44	0.71–4.37	1.19
Free T4 (ng/dL)	1.12, 39	0.79–1.62	0.23
αTPO (IU/mL)	81.30, 46	0–150	120.78
αTG (IU/mL)	715.34, 44	0–24,480	3,685.8

immunoglobulin subclass to be abnormal was IgM, with 19 % of patients having a level higher than the upper limit of normal. However, the mean value of 131.9 (normal 50–196) mg/dL was well within the normal range (Table 1).

Endocrine data

The mean TSH value was 1.99 μU/mL. Mean free T4 was 1.12 ng/dL (Table 1). One patient had briefly been on levothyroxine prior to the study despite having normal TSH, presumably because of the presence of a goiter and thyroid autoantibodies as well as prominent fatigue. Thyroid hormone supplementation had not improved her symptoms. The αTPO was elevated in 63 %, and αTG was high in 86 % of subjects. Both were above normal in 55 %.

Arthritis

Twelve patients (26 %) had active synovitis, 2 (4 %) with a pattern resembling seronegative rheumatoid arthritis but with prominent spinal degenerative disk disease (DDD) and fibromyalgia syndrome. Back pain was historically significant enough to warrant radiographic imaging, which in turn showed significant spinal DDD in 45 % of patients and was an active problem in 33 %. Thus, spinal pain followed polyarthralgias (98 %) and fibromyalgia (59 %) as the commonest clinical presentation of CLT (Table 2). Thirty-one out of 40 patients (78 %) had radiographic evidence of osteoarthritis in the hands, shoulders, knees, hips or spine, and overall 85 % of those with radiographic data had some radiographic evidence of osteoarthritis (Table 2). The mean age of this group with osteoarthritis on X-rays was 51.2 years.

Table 2 Clinical presentation and radiographic data of study cohort

Clinical presentation, *n*	Present (%)
Polyarthralgia, 46	45 (98)
Hand and/or wrist synovitis, 46	12 (26)
History of spinal DDD, 40	18 (45)
Joint distribution, 46	
Pain in small joints of the hands	31 (67)
Knee pain	13 (28)
Knee effusion	1 (2)
Generalized joint pain (both peripheral and axial)	13 (28)
Low back pain	10 (22)
Shoulder pain	4 (9)
DIP pain	1 (2)
Subacromial bursitis	1 (2)
Fibromyalgia, 46	27 (59)
Mild	2 (4)
Moderate	22 (48)
Severe	3 (7)
Myalgia/myositis, 46	6 (14)
With mild CPK elevation	1 (2)
Radiographic arthritis, 40	
Any osteoarthritis findings	35 (88)
Cervical DDD	12 (30)
Lumbosacral DDD	9 (23)
Cervical or lumbar DDD	18 (45)
DIP arthritis	3 (8)
Joint space narrowing	9 (23)
Spinal stenosis	4 (10)
Evidence of spinal surgery	2 (4)

Fibromyalgia

Fibromyalgia syndrome was present in 27 out of the 46 patients (59 %) and was mild in 2 (4 %) and moderate in 22 (48 %). It was severe in 3 (7 %) subjects who were unable to work because of the condition (Table 2). There was no correlation between the presence of fibromyalgia and the presence of synovitis.

Rheumatic serologies

Rheumatoid factor was very low titer positive in 4 out of 46 (8.7 %) patients. Anti-citrullinated protein antibodies (ACPA) were negative in all patients. The ANA was positive in 11 out of 45 patients (24 %). The highest dilution was 1:160, with lower titers in 73 % of the patients. Speckled and homogeneous patterns (2 homogeneous and 3 speckled) were the most common when the intensity was high enough for a pattern to be read. Other autoantibodies were uncommon and did not show any clear patterns (Table 3).

Table 3 Autoantibody profile of study patients

Serological finding, *n*	Present (%)
Rheumatoid factor, 46	4 (8.7)
ANA, 45	11 (24)
Pattern	
Speckled	3 (7)
Homogeneous	2 (4)
ANA titer	
Weakly positive	1 (2)
<1:40	3 (7)
1:40	2 (4)
1:80	2 (4)
1:160	3 (7)
Other autoantibodies	
ACPA, 43	0 (0)
Anti-RNP	1 (2)
Anti-La	1 (2)
Anti-parietal cell antibody	1 (2)
Anti-gliadin IgA	1 (2)
Low serum complement C3 (associated with heavy proteinuria)	1 (2)

Associated autoimmune conditions, apparently in remission and obtained by history alone, included myasthenia gravis never previously treated, hyperparathyroidism status post-hyperparathyroidectomy and hyperthyroidism treated with propylthiouracil (PTU). There was also a case of active pernicious anemia and another of membranoproliferative glomerulonephritis in clinical remission. Two patients with ANAs had UCTD.

Patients with active viremia were excluded from the study, but there was one patient with inactive hepatitis B and C, and another with HIV with an undetectable viral load on highly active antiretroviral therapy (HAART).

Non-arthritic findings

Fatigue was a presenting complaint in 10 out of 40 (25 %) patients in whom the finding was elicited. One patient had severe chronic fatigue syndrome, while the finding was mild to moderate in 8 (20 %) and severe but not chronic in 1 (2.5 %). Other findings included alopecia in 2 out of 39 patients (5 %), myalgias in 6 out of 44 (14 %), dry mouth in 24 %, dry eyes in 13 % and Raynaud's phenomenon in 28 %. Unlike the case in WDCTD, where these findings can be severe and sometimes debilitating, the presentation in this cohort of patients was generally mild. Morning stiffness was minimal in 4 %, lasted less than 30 min in 33 %, was between 30 and 60 min in 11 % and exceeded 60 min in 9 % of subjects with a range from minimal (4 %) to lasting all day (4 %). It was absent in 43 % of patients (Table 4). One patient developed subclinical hypothyroidism during follow-up. No patient became frankly hypothyroid.

Table 4 Non-articular presenting complaints of study patients and presence of family history of autoimmune disease

Non-articular finding, *n*	Present (%)
Fatigue, 40	10 (25)
Raynaud's phenomenon, 46	13 (28)
Dry eyes, 46	6 (13)
Dry mouth, 46	11 (24)
Morning stiffness, 46	26 (57)
Minimal	2 (4)
Mild- <30 min	15 (33)
Moderate- 30–60 min	5 (11)
Severe- >60 min	4 (9)
Alopecia, 39	2 (5)
Neck pain, 46	3 (7)
Sciatica, 46	2 (4)
Developed subclinical hypothyroidism, 46	1 (2)

Family history

A family history of thyroid disease or connective tissue disease was present in 16 and 28 % of patients, respectively, who had knowledge of their rheumatologic and autoimmune family history. Rheumatoid arthritis (22 %) was the commonest connective tissue disease recalled, and lupus was present in 6 % who had a known history. Family history was unknown in 44 % of cases. Raynaud's phenomenon was present among 2 siblings of one patient.

Comorbidities and other autoimmune disorders with possible rheumatic manifestations

With the exception of one patient with pernicious anemia with anti-parietal cell antibodies and another with a prior diagnosis of membranoproliferative glomerulonephritis with significant proteinuria but with clinically inactive nephritis, the other autoimmune disease noted above were in remission and none of these conditions were known to produce rheumatic manifestations. One patient had had a history of endocarditis, which was also without known sequelae.

Clinical correlations

There was no correlation between αTPO and αTG levels. There was a positive correlation between TSH levels and the αTPO titer. However, there was no correlation between

Table 5 Spearman's rank correlations of thyroid autoantibodies with clinical findings

Correlation, *n*	Spearman *r*	95 % confidence interval	*P* value
Age versus αTPO, 46	0.1194	−0.1857–0.4034	0.4294
Age versus αTG, 44	−0.1644	−0.4472–0.1482	0.2861
BMI versus αTPO, 46	0.0696	−0.2337–0.3606	0.6457
BMI versus αTG, 44	−0.1394	−0.4265–0.1731	0.3667
ESR versus αTPO, 44	0.1642	−0.1484–0.4470	0.2868
ESR versus αTG, 42	0.0032	−0.3095–0.3153	0.9841
FMS versus αTPO, 46	0.0416	−0.2600–0.3359	0.7836
FMS versus αTG, 44	−0.1646	−0.4473–0.1480	0.2856
Morning stiffness versus αTPO, 45	0.1499	−0.1591–0.4321	0.3257
Morning stiffness versus αTG, 43	−0.1754	−0.4593–0.1409	0.2605
Synovitis versus αTPO, 46	0.0951	−0.2092–0.3827	0.5294
Synovitis versus αTG, 44	−0.1281	−0.4170–0.1842	0.4071
αTPO versus αTG, 44	0.0873	−0.2238–0.3823	0.5731
TSH versus αTPO, 44	0.3295	0.02699–0.5767	0.0290
TSH versus αTG, 42	0.1775	−0.1428–0.4642	0.2606

antibody levels and BMI, inflammatory parameters, presence of synovitis, morning stiffness or fibromyalgia syndrome (Table 5).

Discussion

The rheumatic manifestations of CLT have been well characterized and reviewed in the context of clinically significant thyroid disease [21]. There are well-documented studies of a broad range of rheumatic manifestations in patients with frank hypothyroidism in whom no other apparent cause of such findings was identified, which suggests a strong association between hypothyroidism and rheumatic disease [22]. Golding reported that muscle weakness, pain and small joint swelling are not uncommon in hypothyroidism. Furthermore, carpal tunnel syndrome, neck pain, synovitis and myopathy were also noted in the author's personal series [21]. More recent reports have included patients without frank hypothyroidism and found similar evidence of joint pain and other rheumatic complaints [23]. Indeed, such reports, although more frequent today, are not new, and Becker and colleagues noted the link between Hashimoto thyroiditis and musculoskeletal disease several decades ago [24]. Other possible associations reflected in the literature include calcium pyrophosphate dehydrate deposition disease (CPPD), muscle cramping and synovial thickening [22]. However, no study has closely examined the rheumatic presentation of a cohort of CLT patients with normal functioning thyroid status. The current study examined 46 consecutive patients in usual care with abnormal thyroid autoantibodies but with normal thyroid function who were referred to a rheumatology practice, and characterized their clinical presentation. A number of novel conclusions were reached which suggest that rheumatic manifestations occur in CLT patients with normal thyroid function. The spectrum of clinical presentations in our cohort mirrors that described in the literature for patients with hypothyroidism and subclinical hypothyroidism, with a significant proportion showing classic osteoarthritis changes [21].

Osteoarthritis is well described in patients with CLT. Interestingly, in addition to the classic distribution of osteoarthritis including the hand and knee arthritis, spinal DDD was especially common in our group (45 %) and was severe enough for 2 patients to have had spinal surgical intervention. Four patients, one of whom had had spinal surgery, had MRI evidence of spinal stenosis (two cervical and two lumbar). We believe this finding is significant since this relatively high frequency is not reflected by the current literature looking at historical controls [25–27]. Clearly, further work is needed to better define the association and note any association in turn of spinal DDD with fibromyalgia as a cause of secondarily generalized pain. Less common sites of osteoarthritis noted radiographically included the hands and wrists, knees, shoulders, ankles and distal interphalangeal (DIP) joints.

The triad of Thyroiditis-Related Inflammatory Arthritis and spinal DDD, conveniently called TRIAD here, is easily confused with classic seropositive rheumatoid arthritis. Two of the 11 patients with synovitis presented in this fashion. In our experience, it differs from rheumatoid arthritis in its involvement with the DIPs, the prominence of arthritis in the cervical and lumbar spines with degenerative disk disease and the presence of CLT. It is also associated with negative ACPA and serum rheumatoid factor antibodies. Furthermore, like the rest of the arthritis that characterizes CLT, it is non-erosive. Musculoskeletal ultrasound performed on one patient clearly demonstrated the inflammatory nature of this complication of CLT from the presence of positive Doppler signals at both wrists. Enthesitis was also found, an uncommon finding in rheumatoid arthritis. Both our patients also had significant fibromyalgia syndrome and thus required immunosuppressive treatment for the arthritis as well as medication for the fibromyalgia.

Fibromyalgia was the most common pattern of chronic pain, and 59 % of study subjects had fibromyalgia syndrome (Table 2). This association with CLT has been noted elsewhere and warrants further investigation [13]. It is unclear whether antibody levels correlate with the presence

or severity of fibromyalgia syndrome and whether thyroidectomy with an accompanying fall in antibody levels might be curative [13, 28, 29]. This study did not show a correlation between thyroid antibody titers and the presence of fibromyalgia but is a small study not powered to address that question. Obvious questions that can be asked concerning this subset of fibromyalgia patients given the overall poor response of fibromyalgia patients to therapy include the following: (1) Why don't a significant proportion of antibody-positive patients develop fibromyalgia? (2) Is there some other as yet uncharacterized autoantibody that is involved in the pathogenesis and correlates strongly with the presence of fibromyalgia? (3) If immunologically mediated, is fibromyalgia treatable with thyroidectomy or immunomodulatory treatments that can reduce autoantibody production, like anti-CD 20 therapy? (4) Is fibromyalgia pain augmented by inflammation in the specific case of CLT and will anti-inflammatory treatment ameliorate the pain?

Bazzichi et al. [28] showed a 33 % incidence of fibromyalgia in Hashimoto thyroiditis patients without subclinical hypothyroidism. The higher percentage with fibromyalgia in the current study might be due to referral bias. However, reliable estimates of the prevalence of fibromyalgia in CLT are lacking due to the absence of population-based studies. Further studies are needed to determine the prevalence of fibromyalgia in this population and the relationship with anti-thyroid autoantibodies.

The systemic autoimmune nature of the findings in this study population is suggested by the presence of multiple autoantibodies. The commonest autoantibody found in association with the anti-thyroid antibodies was the ANA found in 24 % of patients, almost always in low titer. Rheumatoid factor prevalence was not significantly elevated above background (Table 3). These findings with respect to connective tissue disease autoantibodies in CLT are in keeping with previous work by other authors and suggest that the incidence of rheumatoid factors in CLT in the absence of WDCTD does not differ significantly from the general population [30]. However, ANAs have been found to occur with greater frequency in CLT [31, 32]. To our knowledge, this is the first study which has examined the pattern of ANAs as well as the titers in the subpopulation of euthyroid CLT patients without WDCTD. Although this study is small, our findings suggest that ANAs in CLT without the presence of WDCTD are low in titer and generally of speckled or homogeneous pattern. Other autoantibodies included anti-La antibody, anti-RNP antibody and anti-parietal cell antibody (Table 3). Other autoimmune conditions and phenomena were found clinically, including UCTD in 4 % and Raynaud's phenomenon in 28 %. Morning stiffness, sicca symptoms and fatigue were also commonly present, supporting the presence of a more systemic form of autoimmunity (Table 4). Connective tissue diseases have been described in about 25 % of persons with CLT [33]. Although CLT is defined as a classic organ-specific autoimmune disease, these findings suggest that the full spectrum of autoimmunity should be clinically defined whenever CLT is encountered by the rheumatologist.

The only statistically significant correlation found for the levels of the anti-thyroid antibodies was with the levels of TSH. There was no correlation with clinical presentation in terms of arthritis or fibromyalgia or with inflammatory parameters (Table 5). The correlation between αTPO and TSH has been shown previously with regard to the progression to hypothyroidism. In that pediatric population, there was also a correlation between αTPO and αTG levels [34].

We suspect that the clinical features of this population are frequently explained in terms of other conditions attributed to this age group, including early osteoarthritis, seronegative rheumatoid arthritis and primary fibromyalgia. However, we suggest that CLT presents a unifying diagnosis, is a significant cause of morbidity and disability and deserves closer scrutiny. The true prevalence of rheumatic complaints in patients with CLT should be investigated and the natural history of the disease studied. The appropriate setting for such research would be a large population-based trial such as has been used to study the predictive value of ACPA [35, 36]. The contribution, if any, of CLT to the high incidence of osteoarthritis in the post-menopausal period in women deserves special attention since we noted in our cohort that the mean age of 49.1 years is indeed around the age of menopause. About 10 % of the general population has AITD, making thyroid autoimmunity the commonest form of autoimmune disease [6]. It is known that AITD clusters in families with connective tissue diseases, but its impact on those conditions when it overlaps with them has not been defined [37–39]. The impact of CLT on the severity of fibromyalgia, arthritis and other rheumatic manifestations in such overlap syndromes clearly needs to be elucidated.

Study limitations

The absence of a control group of similarly referred patients with negative thyroid autoantibodies was a limitation of the study as was the referral bias inherent in the study. However, the aim of the study was to characterize a cohort with positive anti-thyroid autoantibodies to identify defining characteristics for further population-based controlled studies. It was recognized that appropriate controls could only be defined in large population-based cohorts. This should be the aim of future research. Comparison to historical controls would suggest that our findings do merit

further study and investigation, particularly in relation to the presence of fibromyalgia, inflammatory arthritis and spinal DDD.

Conclusion

Our data suggest that CLT might be an independent cause of inflammatory arthritis, distinct from classic rheumatoid arthritis. This variant, which we call TRIAD, should be recognized since it might have a less favorable response to traditional rheumatoid arthritis treatments than seropositive rheumatoid arthritis. This study also corroborates previous findings of a high association of fibromyalgia with CLT comparable to that described for other WDCTD including rheumatoid arthritis and systemic lupus erythematosus [29, 40]. It suggests that in the particular case of CLT, the fibromyalgia is not a function of thyroid dysfunction. The study also suggests that osteoarthritis might occur at an earlier age and in an accelerated fashion in the context of CLT, with a possible predilection for the spine [26, 27]. We also observed that other autoimmune phenomena and conditions including UCTD are not uncommon in patients with CLT. A prior diagnosis of systemic lupus by non-rheumatologists due to the presence of a positive ANA with rheumatic manifestations was not infrequent, causing patients unneeded stress and anxiety. The study suggests that a subset of euthyroid CLT patients might have a generalized autoimmune process that forms part of the continuum of connective tissue diseases with significant rheumatic manifestations.

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