Review

Rheumatic Manifestations of Autoimmune Thyroid Disease: The Other Autoimmune Disease

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ABSTRACT. Autoimmune thyroid disease (AITD) is an inflammatory thyroiditis that in some cases is characterized by lymphocytic infiltration of the thyroid gland, also referred to as chronic lymphocytic thyroiditis or Hashimoto thyroiditis. Hashimoto thyroiditis is one of the commonest causes of hypothyroidism. Hypothyroidism has been associated with osteoarthritis (OA) and inflammatory forms of arthritis and with several well defined connective tissue diseases, which in turn can cause arthritis. The presence of arthritis in patients with AITD with normal thyroid function is now being increasingly recognized. There is also considerable evidence to suggest that AITD is highly associated with fibromyalgia syndrome. We review the current literature on the rheumatologic manifestations of AITD and describe the features in its presentation that set it apart from other forms of autoimmune arthritis. (First Release April 15 2012; J Rheumatol 2012;39:1125–9; doi:10.3899/jrheum.120022)

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Autoimmune thyroid disease (AITD) denotes a spectrum of immunological disorders of the thyroid gland that includes Graves' disease and chronic lymphocytic thyroiditis (CLT); the latter is also referred to as Hashimoto disease[1]. There is considerable overlap in the clinical presentation of these disorders. Graves' disease is characterized by production of antibodies against thyrotropin receptor[2], activation of thyroid follicular cells, modest infiltration of the thyroid gland by lymphocytes, and hyperthyroidism. In contrast, patients with CLT may experience either hyperthyroidism or hypothyroidism, with hypothyroidism being the dominant characteristic. CLT is often associated with both autoimmunity and various forms of arthritis, and is the focus of this review.

Histopathologically, CLT is typified by impressive lymphocytic infiltration of the thyroid parenchyma, followed by the appearance of Askanazy cells, cellular destruction, and eventual fibrosis[3]. Immune activation initially occurs through MHC class II expression, in the form of HLA-DR molecules on thyrocytes. Histologically, there is T cell infiltrate, subsequent establishment of lymphoid follicles, and eventual thyroid cell destruction[4].

Clinically, the majority of patients with CLT have some degree of thyroid enlargement on physical examination. Morphological changes in the thyroid gland can also be appreciated using musculoskeletal ultrasound in patients with or without an appreciable goiter. Thyroid hypoechogenicity is common, a finding that clinically assists in the diagnosis[5]. Anti-thyroid peroxidase (anti-TPO) antibodies are expressed in 90% to 95%, and anti-thyroglobulin (anti-TG) antibodies in about 20% to 50%, of patients with CLT. A minority of patients express thyrotropin receptor antibodies, but are not considered to have Graves' disease based on histopathology and hypothyroidism; in many cases the thyrotropin-directed antibodies seen in CLT are actually blocking antibodies that can contribute to hypothyroidism. Placental transfer of these thyrotropin receptor-blocking antibodies during the perinatal period can cause transient hypothyroidism in infants born to mothers with CLT[1].

Although biopsy evidence of autoimmune thyroiditis was important in the past, the presence of clinical, biochemical, and ultrasound findings in the absence of tissue sampling establishes the diagnosis of CLT in current clinical practice[6]. Positive antinuclear antibody (ANA) test results are common in both Graves' disease and CLT, not only because of the common association of AITD with other autoimmune diseases, but also in the absence of overlapping autoimmune or connective tissue diseases (CTD)[7].

Estimates of the incidence and prevalence of CLT vary greatly, but one study of an iodine-replete population estimated the prevalence to be about 10%[6], a number that compares well with those from Western sources. The prevalence of hypothyroidism is about 2%. The characteristic overrepresentation of women in many autoimmune diseases is seen as well in AITD in a ratio of about 5:1, regardless of thyroid function[3].

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AITD is the commonest form of autoimmune disease, often described as the prototypic single-organ directed autoimmune disease, but is also increasingly recognized as occurring in association with other forms of autoimmune disease[8]. The reason for this overlap is unclear and is only partially explained by our current understanding of the genetics or pathogenesis of these diseases[9].

It is well known that hypothyroidism is associated with increased incidence of arthritis. Both OA and inflammatory forms of arthritis have been described[10]. The incidence of other well defined CTD is also increased in patients with AITD[11,12]. It is therefore difficult at times to differentiate between arthritis attributable to AITD per se and other forms of arthritis co-occurring with AITD. The presence of arthritis in the context of hypothyroidism has been studied, and many reports examine the possible role of elevated levels of thyroid-stimulating hormone (TSH) in arthritis pathogenesis, since thyroid hormone replacement therapy and return of TSH to normal levels has been found to reverse arthritis in some of these cases[13,14]. The possibility of arthritis existing in the absence of hormonal imbalance, but in the context of AITD not related to other CTD, has been less fully explored. In recent years the association of fibromyalgia (FM) with AITD, in particular CLT, has been reported and is thought to be as high as 30% to 40%[15]. Many of the patients with FM have no evidence of hormonal imbalance.

GENETICS OF AITD

The role of genetics, if not always the precise genetic mechanisms, is well established in several autoimmune diseases[16]. That genetics is important in AITD is evidenced by the fact that AITD is predominantly a disease of women. AITD is also clearly more prevalent in the relatives of affected patients, with a high concordance rate in homozygous twin studies[17]. Indeed, it is often the most common autoimmune disease in these families, and a thorough history elucidating the presence of AITD in a family is often a clue to establishing the presence of other autoimmune diseases.

Important findings from genome-wide association studies (GWAS) of autoimmune diseases include the observation that more and more genes with innate immune functions are being implicated. It is also increasingly obvious that, in any one individual, multiple genes working together with various poorly understood environmental factors lead to the breakdown of immune tolerance and the generation of autoimmunity[16]. This may explain the difficulty in defining the genetics of autoimmunity, since different permutations of polygenic variations occurring in different families may make it hard to isolate single candidate genes using GWAS. Thus, it is no surprise that no single candidate gene has yet been conclusively shown to predispose to AITD. Within the family of AITD, the strongest association is within the class II DR/DQ alleles. However, the genetics of Graves' disease differs from that of CLT. Genetic variation in the gene for cytotoxic T lymphocyte antigen-4 has been found to be associated with Graves' disease but not with CLT[17]. Similarly, protein tyrosine phosphatase-22 has been identified as a susceptibility locus in Graves' disease but not in CLT[17].

That many autoimmune diseases appear to be antigen-driven, and are inadequately explained by genetics alone, suggests an important role for environmental factors either as etiological agents or as modulators and modifiers of the autoimmune process. Viruses have long been sought as culprits in this regard but have not been convincingly implicated, to the extent that active infection is rarely associated with the onset of full-blown autoimmune syndromes. Latent infection has been suggested as possibly driving some forms of autoimmunity, and several viruses have been suspect in the particular case of AITD, as reviewed by Desailloud and Hober[18]. Other environmental influences, including the availability of iodine or drugs including amiodarone, interferon-α therapy, interleukin 2, and lithium can lead to thyroid cell destruction and thyroiditis with clinical hyperthyroidism or hypothyroidism. These forms of thyroiditis may be associated with the presence of anti-TPO antibodies and possibly unmask AITD in susceptible individuals[1].

ARTHRITIS IN AITD

Arthropathy in hypothyroidism has been recognized as a phenomenon for over 100 years[19]. Associations with carpal tunnel syndrome and chondrocalcinosis have also been described, as well as with shoulder capsulitis[20]. Other well described musculoskeletal complaints include neck pain, generalized stiffness, and myopathy. Anterior chest wall pain has also been reported. It is unclear how many of these symptoms are actually a reflection of the FM reported in more recent publications[21].

Gillan and coworkers[13] described a case of bilateral knee arthropathy and effusions in a 26-year-old hypothyroid woman with no morning stiffness or constitutional symptoms. Synovial fluid was noninflammatory, with a markedly increased viscosity and strongly positive string test. The effusions resolved with thyroid hormone replacement. This form of arthritis is frequently described as an accompaniment to hypothyroidism. It has been reviewed by Bland and others[21] and typically affects the knees, metacarpophalangeal joints, proximal interphalangeal joints, and metatarsophalangeal joints without the presence of inflammatory synovitis. There is thought to be a TSH-dependent increase in hyaluronic acid and proteoglycan synthesis in this subgroup of hypothyroid patients. Thus TSH elevation seems to be necessary for the presentation. This observation also supports the response to thyroid hormone replacement, with concomitant TSH suppression[21].

Becker, *et al*[10] noted a more diverse presentation of arthritis in patients with Hashimoto thyroiditis some

decades ago. They also noted an association with what they termed "secondary fibrositis," which overlaps with our current definition of FM. A report by LeRiche and Bell fleshed out these other forms of arthropathy by documenting a form of seronegative rheumatoid arthritis (RA) that, unlike the aforementioned arthropathy, could be found in euthyroid patients[22]. This form of arthritis was inflammatory and differed from another clinical subset of AITD-related arthropathy, which they presumed to be seropositive RA, in its HLA association (HLA-DR2 in the former versus HLA-DR4 in the latter), seronegativity, nonerosive arthritis, and absence of nodulosis. Thus it appeared to be a distinct form of inflammatory arthritis, which unlike the previously described noninflammatory arthropathy did not respond to thyroid hormone supplementation.

Punzi and co-workers described clinically distressing polyarthralgias in a subset of 20 patients with CLT without any known rheumatic disease[23]. The total number of referrals of patients with CLT and rheumatic complaints was 130, of whom 110 had a known rheumatic disease. Eight of the 20 patients described were euthyroid. There was a significant association between the number of joints affected by pain and antimicrosomal antibodies, erythrocyte sedimentation rate (ESR), and TSH levels, but not anti-TG antibody levels. ANA was positive in 8 of the 20 patients and did not correlate with clinical findings. Improvement was described in the hypothyroid subset comprising 10 of the 20 patients treated with thyroid hormone for an observation period of up to 24 months. This was thought to be significant by the authors, but it is unclear if the improvement also reflects either the natural history of the disease, or significant changes to the thyroid autoantibody titers as a result of the natural progression of the disease since serial measurements were not documented[23].

Although, as stated above, AITD is the commonest organ-specific autoimmune disease, accumulating evidence suggests that it very frequently occurs in the context of a more generalized autoimmune process. One group showed a 51% association of Hashimoto thyroiditis with well defined systemic autoimmune diseases including mixed connective tissue disease, Sjogren's syndrome, systemic lupus erythematosus, RA, systemic sclerosis, and polymyositis/dermatomyositis[11]. These findings have been duplicated in other populations and firmly establish the association of AITD with other forms of arthritis caused by CTD[8].

Conversely, the incidence of AITD is increased in at least some patients identified as harboring other autoimmune diseases[8,24]. In a study assessing thyroid function, as well as the prevalence and clinical significance of antithyroid autoantibodies in patients with RA, Atzeni, *et al*[25] reported an increased prevalence of antithyroid antibodies in patients with RA, with a low prevalence of hormonal alterations. The cohort comprised 70 patients with RA as defined by the 1987 American College of Rheumatology classification criteria for RA. In all, 22.9% of patients were positive for anti-TG antibody, and 37.1% had anti-TPO antibodies. Five patients (7.1%) had TSH levels that were slightly elevated in the range of 4.52 to 15.65 IU/ml. Three patients (4.2%) had increased TSH levels associated with normal free T4 levels and showed subclinical hypothyroidism. Only 2 of the patients (2.8%) had clinical hypothyroidism and were receiving treatment with L-thyroxine. The authors found no statistically significant difference between the thyroid antibody-positive group and the thyroid antibody-negative group with regard to swollen joint count, tender joint count, medication use, and inflammatory markers (ESR, C-reactive protein)[25]. However, they showed that there was a significant correlation between anti-TG antibody levels and ESR. Further, among those patients with RA with positive anti-TG antibody and anti-TPO antibody levels, 75% and 69%, respectively, were ANA-positive versus 55% and 54% without those antibodies. The trend, however, did not reach statistical significance for the small number of patients enrolled in the study[25].

Lazurova, *et al* found the incidence of AITD in SLE and RA to be 24% in both diseases and 8% in their control population[7]. A positive ANA test was present in 45% of AITD subjects versus 14.7% of controls in the same study. Undifferentiated (U) CTD, perhaps the commonest presentation of CTD, was not studied, and the prevalence of AITD in patients with UCTD has not been reported. In an intriguing study, Blake, *et al* investigated thyroid microsomal and thyroglobulin autoantibody activity; in synovial fluid studies 34 of 50 patients with RA, ankylosing spondylitis, OA, or gout were positive, while in serum studies only 4 of the patients were positive (and at lower concentrations), suggesting that thyroid autoantibodies may be produced locally in the joints of these patients[26]. The implications for how a more generalized autoimmune process might develop have not been comprehensively explored. Still, studies such as this suggest that autoimmunity, including thyroid autoimmunity, might be a more systemic process than previously thought. These studies speak to the need to define the full spectrum of autoimmunity in any given patient with arthritis, and conversely, in patients with AITD with rheumatic complaints referred to the rheumatologist.

FM IN AITD

As mentioned, the association between AITD and FM has been recognized for decades and was first described in the context of fibrositis, an antiquated term whose scope overlaps our current definition of FM[10]. However, the association has remained a muted reference in the literature until recently, when it was rejuvenated by several authors[15,27,28]. That it has not been more widely propagated is astonishing given that the prevalence of FM in AITD is reportedly in the range of 30% to 40%[15,27,28]. Because so few authors have reported this relationship, it is unclear what characteristics

of thyroid autoimmunity predispose to the development of FM. This raises several questions: Does that subset of patients most likely to have FM have higher inflammatory markers? Do they have a positive ANA or higher antithyroid autoantibodies? Are any of those particular autoantibodies more closely associated with the presence and persistence of FM? Further, could a neurotropism displayed by a known or as yet unrecognized antibody explain the heightened pain sensitivity in FM associated with AITD, or is there perhaps molecular mimicry that targets neural tissue?

FM frequently complicates several systemic autoimmune diseases and testing for AITD might be an important part of defining the risk factors for FM in such patients. It is also important to note that the symptom complex associated with hypothyroidism tends to overlap that of FM. Thus insomnia, real or perceived weight gain, chronic fatigue, headaches, irritable bowel syndrome, and arthralgias are common to both syndromes and sometimes persist after treatment of hypothyroidism. In a small minority of cases treatment failure can be related to resistance to thyroid hormone. The vast majority of such cases are related to mutations in the thyroid hormone receptor-ß alleles. Several other genes with gene products that are important in the signaling of thyroid hormone have been implicated in generating resistance to thyroid hormone. Patients typically have elevation of serum thyroid hormone levels in the presence of inappropriately normal serum TSH levels[29]. However, in some instances no clearly defined genetic basis for thyroid resistance can be found[30]. It has also been hypothesized that less dramatic forms of peripheral resistance to thyroid hormone might be acquired and might be influenced by drugs, autoantibodies, or environmental agents[31]. These authors have suggested that similarly to the concept of insulin resistance, peripheral acquired thyroid hormone resistance might be far more common as a cause of persistence of symptoms in patients treated with thyroid hormone than the rare genetic defects that occur with a frequency of only about 1 in every 40,000 live births[29]. Such a concept of thyroid hormone resistance would naturally constitute an important differential diagnosis of FM.

The enrichment of FM in AITD is a phenomenon that deserves closer scrutiny and investigation, not only because the reported association is so strong but also because further understanding of the pathogenesis might shed light on the general pathobiology of FM.

SPINAL DEGENERATIVE DISC DISEASE IN AITD

The possibility of spinal degenerative disease in CLT has been lumped together with reports of neck pain in the literature[21]. In our own experience of patients' autoimmune thyroiditis in usual care, 29 patients with a diagnosis of autoimmune thyroiditis with no evidence of thyroid dysfunction were seen in our outpatient rheumatology clinic for a primary complaint of pain (arthralgias, myalgias) between 2006 and 2009. All 29 patients were women with an age range from 23 to 79 years. All were clinically euthyroid and all but 3 tested negative for ANA. Of the 3 patients that had positive ANA titers, none had any underlying autoimmune rheumatologic condition clinically or serologically. All patients had elevated levels of anti-TPO or anti-TG antibodies. None of the patients had rheumatoid factor or anticitrullinated protein antibodies (unpublished data).

Degenerative disc disease of the cervical and/or lumbar spine was the most common rheumatologic finding (18/29) in this cohort, while the second most common finding was FM syndrome (11/29). Other commonly seen radiographic findings included osteoarthritic changes in the hip joints, seen in 4 patients, knee OA in 3 patients, and distal interphalangeal joint degenerative changes in 3 patients. We noticed an interesting pattern of cervical spine involvement in this cohort. In contrast to the distribution normally described in RA, spinal disease in these patients spared the C1-C2 articulation but affected the C3-C4, C4-C5, and C5-C6 articulations (unpublished data). These findings suggest a possible correlation between autoimmune thyroiditis and spinal degenerative disc disease, which warrants more detailed, controlled studies and systematic exploration. It also confirms previous reports of a very strong association with FM.

CONCLUSIONS

The arthritis associated with AITD was previously reported as occurring in the form of OA and noninflammatory joint effusions. More recently it has become clear that arthritis may exist in the context of CTD frequently found to co-occur with a condition that had been thought of as the classic organ-specific disease. Further, it would appear that AITD in the absence of hypothyroidism or overlap with systemic autoimmune disease is also associated with seronegative arthritis mimicking RA but displaying a nonerosive phenotype. Other reasons why the rheumatologist might see a patient with AITD include referrals for a positive ANA with or without signs or symptoms of a UCTD. FM is also a frequent accompaniment of AITD. Thus it would appear that AITD shares with other endocrine disorders, such as acromegaly, diabetes, and hyperparathyroidism, several rheumatic complications[21]. However the etiology of these conditions is more complex, with both hormonal and immunologic influences having been postulated[21,22]. The practicing rheumatologist therefore needs to be acutely aware of these associations since he or she might well be the initial caregiver for a patient with AITD. The investigation of such patients should involve the elucidation of the full spectrum of autoimmunity if the prognosis and further management are to be comprehensively defined and achieved, respectively. Autoimmunity affecting the thyroid gland has historically been overlooked by rheumatologists, but it is becoming more apparent that there are several consequences

to this process that frequently come to the attention of the practicing rheumatologist. Further, it can be argued that the thyroid gland is a rather accessible organ and should be the focus of more concerted efforts to study the genetics and etiopathogenesis of organ-specific and systemic autoimmunity at the translational level and at the level of fundamental basic research. Perhaps it is time for AITD to emerge out of the shadows and no longer be seen as the "other autoimmune disease."

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