“Three in One” - Polyautoimmunity with Multiple Autoimmune Syndrome

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Abstract
Autoimmune disease (AD) may well start off as a single diagnosis and over the years develop into polyautoimmunity and even multiple autoimmune syndromes (MAS) seen in the same patient, as new clinical symptoms and laboratory findings show up in the course of disease. We present a case of MAS who was initially diagnosed to have autoimmune thyroid disease (AITD) – hypothyroidism. She was then evaluated for persistent mild to moderate iron deficiency anemia, unintentional weight loss along with skin rash and diagnosed to have celiac disease and undifferentiated connective tissue disease (uCTD).

Introduction
Autoimmunity is an immune response directed against an antigen within the body of the host whereas autoimmune disease is a pathologic condition caused by the adaptive autoimmune response. The first step in the diagnosis of these diseases is usually the demonstration of autoantibodies. However, the mere presence of autoantibody does not necessarily establish a cause-and-effect relationship, since the autoantibodies may be the result, not the cause, of the disease process. The antibodies may present many years before the clinical appearance and diagnosis of many connective tissue diseases. Combined with genetic information or family history, the presence of autoantibodies may be highly predictive of the later onset of an autoimmune disorder.1,2

Polyautoimmunity which encompasses the concept of a common origin of these diseases, is defined as presence of more than one AD in a single patient. When three or more ADs coexist, it is called multiple autoimmune syndrome (MAS), which represents the best example of polyautoimmunity as well as the effect of a single genotype on diverse autoimmune phenotypes.

This is a clinical case of a mature adult female patient, now 26 years old with a family history of Type 2 diabetes mellitus (T2DM) and hypertension in both parents and autoimmune thyroid disease (AITD) in sibling and mother. In 2012 she was initially diagnosed with hypothyroidism and has by now diagnosed with Celiac disease and early uCTD.
A 23 year female, was diagnosed with thyroprivic hypothyroidism and moderate anemia in June 2010 and has a history of not gaining weight. She weighed 34 kg then with a body mass index (BMI) of 14.2 kg/m². She was started on 50ug of Levothyroxine with regular monitoring of thyroid functions and has been taking iron-vitamin and calcium supplements intermittently for persistent anemia and body-aches. Despite titrating her levothyroxine dosage she always had low FT4 and raised TSH. Her thyroid functions, levothyroxine dosage, hemoglobin, hematocrit and actual body weight are tabulated in Table 1.

She has a family history of AITD-hypothyroidism (mother/sister), along with T2DM and Hypertension in both parents. She attended clinic on 22.08.2016 with complaints of weakness, loss of appetite, diffuse aches, un-intentional weight loss of around 8 kg in last 2-3 months, and developing erythematous and itchy skin on exposure to sun. She has mild pallor and normal skin clinically. She had no history of Raynaud phenomenon, inflammatory arthritis, dryness in oral cavity or chronic cough. Her vital parameters and systemic examination were essentially normal. She was evaluated and had moderate iron deficiency anemia with high Hb and TPO antibodies. She was admitted on 22.08.2016 for parenteral iron therapy and upper GI endoscopy (UGIE) with duodenal biopsy. Her other reports are mentioned in table 2. Figure 1 shows findings on histopathology of duodenal biopsy and UGIE. Her X-ray chest, ultrasound of whole abdomen, bone mineral densitometry and routine urine examination were normal. She was diagnosed with Celiac disease and AITD. In view of her skin rash and aches she was further investigated for other possible concurrent ADs and was confirmed to have early undifferentiated Connective tissue disease (eUCTD) with positive ANA, SS-A and Anti centromere antibodies. In follow up after 3 months, she has gained 10 kg in body weight, her levothyroxine dosage has been reduced to 100ug with normal thyroid functions, and hemoglobin has improved to 13.6 gm/dl. She refused for a repeat UGIE.

**Discussion**

Herein, we have reported a case of polyautoimmunity, a term that was used for the first time by Sheenan and Stanton-King. There is strong evidence that ADs share several clinical signs and symptoms, pathophysiological mechanisms, environmental and genetic factors, and this fact indicates that they have a common origin, which has been called the autoimmune tautology. Polyautoimmunity may influence on the severity of ADs. Familial autoimmunity and female gender are confirmed risk factors for polyautoimmunity.

Celiac disease (CD) is frequently accompanied by a variety of extra digestive manifestations, thus making it a systemic disease rather than a disease limited to the gastrointestinal tract. It is a permanent intolerance of dietary gluten leading to mucosal damage in susceptible individuals, characterized by inflammation, crypt hyperplasia and villous atrophy which regress on withdrawal of gluten from the diet. The clinical presentation of CD has now moved from overt malabsorption in childhood towards milder symptoms or atypical features in adult life. Clinicians must remember that CD may present...
with extra intestinal manifestations, and associated illnesses may appear both at the time of diagnosis and throughout the evolution of the disease. The case discussed has been diagnosed with Hypothyroidism 6 years back and despite titrating levothyroxine dosage had persistently low FT4 and high TSH. She also had persistent mild to moderate anemia and unintentional weight loss (despite hypothyroidism) and malabsorption/CD was never thought.

CD has been found at an increased rate in patients with autoimmune thyroid disease with a prevalence ranging from 2% to 7%. The decrease of the thyroid antibodies after 2 or 3 years or the normalization of thyroid function after 1 year of gluten free diet (GFD) has been reported and these results may depend on longer duration of GFD in treated patients with CD. Such associations of AD’s may lead to adverse effects on the growth, metabolism, and fertility. The coexistence of CD and AITD has been explained by several mechanisms such as common genetic predisposition and the association of both diseases with the gene encoding cytotoxic T-lymphocyte-associated antigen-4, a gene conferring susceptibility to thyroid autoimmunity. In addition, it has also been demonstrated that tTG antibodies react with thyroid tissue, and this binding could contribute to the development of thyroid disease in CD.\(^5\)

Presence of diffuse aches and rash on exposure to sun made us to evaluate her for other associated ADs including CTD. Unclassifiable symptoms, no physical examination findings, and serological results suggestive of a CTD lead to diagnoses of an early UCTD. UCTD are those in which signs and symptoms are consistent with a CTD but that do not fulfill the classification or diagnostic criteria for any one of the defined CTDs. In order to fulfill the criteria for UCTD, ANA must be present, along with disease duration of at least 3 years. Cases with a shorter duration should be described as early UCTD. The case discussed had positive ANA and antibodies to Ro/SS-A and centromere. Women with anti-Ro/SS-A antibodies are at increased risk for having a child with neonatal lupus syndrome. Anti-Ro/SS-A antibodies may also be the first detectable auto antibodies that precede the development of SLE in asymptomatic individuals.

There are three phases of UCTD. The initial phase of UCTD may occur many years prior to diagnosis, during which time the patient may be asymptomatic and may lack serum auto antibodies. In the second phase, auto antibodies may appear in the serum despite an absence or paucity of symptoms. The interval between autoantibody appearance and significant symptom onset is highly variable among individual patients and the specific auto antibodies. Finally in the third phase signs and symptoms of the autoimmune disease appear, leading to a definitive diagnosis. A clinical diagnosis of early UCTD may be made in the second phase, and some of these cases may evolve into a definite CTD or may remain undifferentiated. Our patient also evolved into second phase of UCTD over these years. Some antibodies have greater diagnostic value. Among them anticentromere is associated with limited cutaneous systemic sclerosis (CREST syndrome). In a study of 148 UCTD patients with antibodies to SSA, 24 percent developed a defined condition, mainly SLE and Sjögren’s syndrome.\(^5\) Our patient is in second phase of UCTD, has positive anti Ro/SS-A and antimicrosome antibodies and is advised to take hydroxychloroquine tablets and to avoid sun exposure. Finally she will evolves into which AD or remain undifferentiated, cannot be commented at this moment.

The implementation of a gluten-free diet (GFD) improves the overall clinical course and influences the evolution of the associated diseases. In this case, she has gained weight, her thyroid status has normalized and iron deficiency anemia has disappeared.

**Conclusions**

Diverse ADs in the same patient including organ specific and systemic ADs, are true associations as a part of the autoimmune tautology rather than the chance findings.

One should search for well-defined phenotypes by looking for clusters of ADs in the same individual and try to explain their existence by sharing of the same etiopathogenesis rather than a secondary disease. Polyautoimmunity is the term proposed for this association of disorders.

Treatment of CD with a gluten-free diet reduces the recognized complications of this disease (such as malabsorption, and infertility), provide benefits in general health and perhaps life expectancy, improves glycemic control in patients with type 1 diabetes mellitus, enhances the absorption of medications for associated hypothyroidism, iron deficiency anemia and osteoporosis.

A premature diagnosis of one of the discrete rheumatic diseases should be avoided, since the undifferentiated nature of the syndrome usually persists. Among those destined to develop a defined connective tissue disease, which is more common than resolution of the syndrome, evolution generally occurs within two to five years.

**References**