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Transient Anti TG2 Autoantibodies in Systemic Lupus Erythematosus: A Window to Autoimmunity

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Abstract Transient anti transglutaminase2 and anti endomysial antibody elevation in systemic lupus erythematosus is fundamentally thought-provoking with respect to establishment of autoimmunity and its progression. Celiac disease and systemic lupus erythematosus are both relayed within the mosaic framework of autoimmunity. Transglutaminase2 is a multifunctional enzyme, involved in cell biology and survival and is one of the post translational modifiers of protein, enhancing autoimmunity. TG2 and its specific antibodies are heavily involved in celiac disease. TG2 is essential in clearance of apoptotic cells and experimentally participates in systemic lupus-like induction. However, the role of anti TG2 autoantibodies is far from being unraveled. Despite disappearance of these antibodies on gluten containing diet, in the present case, the boy is at risk of developing celiac disease in the future.

Keywords: *tissue transglutaminase, anti-TG2, autoantibodies, systemic lupus erythematosus, celiac disease, autoimmunity*

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1. Introduction

The case report on the transient anti transglutaminase2 (TG2) and anti endomysial antibody (EMA) elevation in systemic lupus erythematosus (SLE) [1] provokes a fundamental reappraisal of autoimmunity and autoimmunogenesis.

The diagnostic challenge of CD in a patient suffering from SLE and secondary antiphospholipid syndrome, with transient positive serum levels of CD -specific antibodies, with an increased genetic risk for CD, demonstrated by HLA-DQ2 positivity, is reported. Several details are worth expanding upon prior to illuminating certain aspects. No intestinal biopsy was performed when CD serology was positive, multiple autoantibodies were elevated on admission (anti-nuclear, anti-dsDNA, anti-histone, antinucleosome, anti-β2glycoprotein, anti-cardiolipin, anti-thyroid peroxidase, anti-TG2 and anti-EMA) and some of these(anti-thyroid,TG2 and EMA) autoantibodies disappeared on gluten containing diet but also under low dose maintenance glucocorticoid therapy. The boy in question represents a realistically clinical complex situation were fluoride SLE, secondary anti-phospholipid syndrome, immunosuppression by steroids, and positive celiac and thyroid associated autoantibodies cohabit together. The following discussion will expand on these aspects.

2. The Boy did not Have CD

The case presented did not fulfill the revised 2012 ESPGHAN criteria for pediatric CD diagnosis [2]. Despite positive HLA-DQ2 and positive EMA, his anti TG2 was positive only X3 ULN, his symptomatology was much more typical for SLE then for CD, and intestinal biopsy was not performed in the presence of positive celiac associated serology. It is obvious that these ESPGHAN criteria do not apply in an immune compromised child, like in the present case. It has been known for many years that systemic steroid therapy induces lymphopenia and suppresses B lymphoplasmocytic secretion of autoantibodies [3]. Further more, immunosuppression can modulate symptomatology and intestinal histology in addition to serological biomarkers. The question arises as to whether the CD or thyroid specific AB would have disappeared in steroid-free situations. It is well known, at least in celiac associated AB, that even on GCD, the autoantibodies might fluctuate, attaining normal levels periodically [4,5].

The Positive HLA-DQ2 in the present case is important, but does not help in CD diagnosis since 30-40% of the populations in western countries are positive. On the contrary, negativity would help much more to exclude CD, since 95% are positive forHLA-DQ2/8.

3. SLE is Prevalent in CD and Vice Versa

Dozens of case reports were described suggesting the association between SLE and CD. It was recently concluded that celiac patients were at a 3-fold increased risk of developing SLE, but the absolute risk was low [6]. In the past we have reported that celiac patients had increased frequency of serum anti-single stranded DNA (14%), anti-double-stranded DNA (23%) and anti-cardiolipin (14%) [7]. More so, it was shown that the anti-DNA idiotype 16/6 Id, originating from a CD girl's serum, was pathogenic and induced experimental SLE [8]. But many other autoantibodies, spanning the entire autoimmune arena, are included in the sera of CD patients [9,10]. CD can masquerade as SLE, or SLE can develop later in the clinical course of CD, even after responding to GFD [10,11].

4. Anti TG2: Bystanders or Pathogenic?

It is difficult to answer this question in the present case report since the CD and thyroid autoantibodies disappeared on steroid therapy and CD was not diagnosed. However, it cannot be ruled out that they will reappear in the future since anti-TG2 antibodies are fluctuant, as mention before, and are predictive. Of not less importance, and possible greater, is the question as to whether the boy had IgA-TG2 deposits in his intestine. Such deposits are present in the small-bowel mucosa at an early stage in the disease when the mucosal morphology is still normal [12].

Endomysial and TG2 antibodies have long been considered to be innocent bystanders in celiac disease. Lately, however, evidence has accumulated on the role of anti TG2 antibodies as modifiers of TG2 enzyme functions. In fact, accumulating data, from cell based experiments, has demonstrated their ability to induce biological effects in many different cell type [13]. Since TG2 post translational deamidation of gliadin peptides is considered to be cornerstone in the activation of the adaptive immune system, and since TG2 has multiple effects on major players in the intestinal innate immune system, and CD anti-TG2 antibodies inhibit TG2 enzymatic activity, those antibodies can be considered as pathogenic [13,14]. They destabilize the integrity of the CD mucosa, thus contributing to CD establishment and progression [15]. Based on the above mentioned knowledge, and even if the autoantibodies have currently disappeared, the present patient should be followed carefully and periodically for CD associated autoantibodies.

5. Does TG2 and/or anti-TG2 Antibody Have a Role in SLE?

In SLE, inadequate removal of apoptotic cells may lead to challenge the immune system with immunogenic self-antigens that have been modified during apoptosis. Development of SLE-like autoimmunity was observed in many mouse models, in which phagocytosis of apoptotic cells was impaired [16]. Increasing evidence suggests that TG2, being a multifunctional protein, is strongly coupled to clearance of apoptotic cells. If anti-TG2 can modify TG2 activity, it is logical to conclude that in the apoptotic domain, it can open a plethora of opportunities for post translational modification of proteins, turning self-peptides from tolerated to autoimmunogenic, in various autoimmune diseases. Specific autoimmune antibodies play a pathogenic role in autoimmune progression, like in CD, dermatitis herpetiformis, type1 diabetes, multiple sclerosis and pemphigus vulgaris. However, this has not yet been shown for SLE. TG2 functions or dysfunctions have not been explored in human SLE. To date, anti-TG2 antibodies have been found at a low rate in SLE patients and mostly have not indicated the presence of CD [17].

6. Conclusions

The case reported by Spârchez M et al [1] represents an interesting clinical dilemma of a transient anti-TG2 antibody surge and positive HLA-DQ2, in a SLE affected child, treated with systemic steroids. CD was not established, according to the ESPGHAN criteria, but a potential risk exist of developing the disease, once off steroids. Multiple aspects of the role of TG2 and anti-TG2 in autoimmunity progression are discussed and set the stage for clinicians to consider associated autoantibodies as potentially pathogenic and not simply as bystanders.

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