The Mosaic of Autoimmunity
A Classical Case of Inhalation of a Polyclonal Activating Factor in a Genetically and Hormonally Susceptible Patient Leading to Multiple Autoimmune Diseases

Daniella Rahamim-Cohen MSc MB BS and Yehuda Shoenfeld MD
Department of Internal Medicine B and Center for Autoimmune Disease, Sheba Medical Center, Tel-Hashomer and Sackler Faculty of Medicine, Tel Aviv University, Israel

Key words: autoimmune disease, polyanethol sulfonate, polyclonal B cell activation, systemic lupus erythematosus

IMAJ 2001;3:381-382

The “mosaic of autoimmunity,” a term coined over a decade ago [1], describes the multifactorial origin and diversity of expression of autoimmune diseases. The term implies that different combinations of the many factors involved in autoimmunity produce varying and unique clinical pictures that represent the wide spectrum of autoimmune diseases. Most of the factors involved in autoimmunity can be categorized into four groups: genetic, immune defects, hormonal, and environmental [1].

The following case report represents a classic example of the concept of autoimmunity developing as a mosaic, and demonstrates how factors from each of the above categories combine to produce a variety of autoimmune diseases in one individual.

Patient Description

A 45 year old non-smoking Caucasian woman had worked as an engineer at an energy research center for 8 years. When she was 30 years old an accident occurred at work and she inhaled polyanethol sulfonic acid. Her past medical history prior to the incident was unremarkable, apart from two hospitalizations. The first, for the investigation of fever when she was 19 years old, revealed increased thyroid iodine uptake and she was treated with thiouracil. Her second hospitalization, at the age of 24, was for abdominal pains. On both occasions her erythrocyte sedimentation rate and differential blood count were considered normal.

Shortly after the aforementioned accident involving PSP she was hospitalized due to inflammation of the right knee and fever, which was treated successfully. However, she subsequently underwent a series of hospitalizations and tests, and within a period of 2 years was diagnosed as suffering from systemic lupus erythematosus, thyrotoxicosis (Hashimoto’s disease), polyarthritis, Raynaud’s syndrome, relapsing polyarthritis, and vasculitis. Her blood results were as follows: antinuclear factor 1:168 (speckled and homogenous), anti-thyroid cytoplasmic titer 1:40, anti-dsDNA 12% in amonium sulphate precipitate (normal 10%), C3 >80 mg/dl (normal 55-120 mg/dl) and C4 16 mg/dl (normal 20-50). In addition, she was found to have hypergammaglobulinemia with immunoglobulin G 1,900 mg/dl (normal 1,250±300 mg/dl), IgA 200 mg/dl (normal 210±50) and IgM 209 mg/dl (normal 125±50 mg/dl). Other antibodies found included: antinuclear, antinuclear microsomal, anti-Tg, anti-parietal, antigliadin, antireticulin, and anti-smooth muscle. ESR and differential blood count were considered normal. Treatment consisted of plaquenil, intravenous Ig and corticosteroids.

Two years ago she was diagnosed with Sjogren’s syndrome, polyneuropathy multiplex, temporal epilepsy and celiac disease with lactose intolerance. Her HLS tissue typing is A2, A3, B8, B14, Bw6, DR3, DR7, DRW53, DQW2.

Comment

The patient described is a middle-aged woman with HLA tissue typing B8/DR3 and mild complement deficiency. The higher propensity of autoimmune diseases in females is well documented and is thought to result from the effects of estrogen (i.e., the hormonal factor) [1]. The HLA B8/DR3 haplotype is recognized as particularly prevalent in SLE (the genetic factor) [1,2]. Furthermore, immune defects such as immunoglobulin abnormalities, complement deficiencies, suppressor T cell defects and spontaneous polyclonal B cell activation are often found in persons who develop autoimmune diseases (immune deficiency factors) [1,2]. Our patient was found to have low levels of C4 and elevated levels of IgG, consistent with abnormalities found in persons with autoimmune disease (humoral and genetic factors).

However, until the inhalation of PSP, an anionic detergent used extensively in microbiology, our patient was in good health. PSP was found to be a potent polyclonal B cell activator in a process dependent on macrophages and macrophage-related factors (the environmental

\[ \text{PSP} = \text{polyanethol sulfonate} \]

Ig = immunoglobulin
ESR = erythrocyte sedimentation rate
SLE = systemic lupus erythematosus
factor) [3]. Polyclonal B cell activation has been recognized as playing a major role in the pathogenesis of autoimmune diseases (mechanisms) [1]. A polyclonal antibody response is mounted against thymus-independent antigen, causing a large number of B cells to proliferate and mature into antibody-forming cells independent of antigen stimulation. In addition, PSP was found to interact with the complement system in a complex manner, inhibiting both classical and alternative pathways of complement activation [4]. It is known that antibody-dependent cell-mediated cytotoxicity and natural killing are inhibited by PSP [5]. Many environmental agents have been implicated in inducing autoimmune diseases, including ultraviolet radiation, infections, drugs, and smoking [1]. It is indeed plausible to consider PSP as an environmental agent that acted as a "trigger" factor causing the immune state of our patient.

While the clustering of more than one autoimmune disease is a well-known phenomenon [1], the clustering of at least five autoimmune diseases in one individual is considered highly uncommon. Thus, in the patient described here it would seem that the combination of genetic susceptibility, female gender and the inhalation of a biologically active substance (a polyclonal activator) constitutes the pieces of the mosaic that presented with the development of an assortment of autoantibodies and autoimmune diseases.

References

Correspondence: Dr. Y. Shoenfeld, Dept. of Medicine B, Sheba Medical Center, Tel-Hashomer 52621, Israel. Phone: (972-3) 530-2652, Fax: (972-3) 535-2855, email: shoenfeld@post.tau.ac.il

---

**Fatal Liver Necrosis Associated with the Use of Nitrofurantoin**

Yeouda Edoute MD PhD, Yuval Karmon MD, Ariel Roguin MD and Haim Ben-Ami MD

Department of Internal Medicine C, Rambam Medical Center and Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

**Key words:** nitrofurantoin, hepatic toxicity, drug-induced liver disease

Nitrofurantoin, a furan derivative, is used primarily in the treatment of urinary tract infection. It has also been found to be appropriate for use in long-term prophylaxis of recurrent UTI in view of its efficacy, favorable safety and tolerability profile [1]. It is rapidly and completely absorbed from the gastrointestinal tract. Reducing enzymes appear to be crucial for its activation. However, it may cause a wide range of adverse reactions. Chronic hepatitis and ensuing liver damage caused by nitrofurantoin toxicity is very rare.

We report the case of a 73 year old woman who had been taking nitrofurantoin as a prophylactic measure for 14 months and developed fatal hepatic necrosis. Another notable feature was positive antinuclear antibodies. Drug-induced hepatic toxicity is reviewed, with emphasis on early consideration in the differential diagnosis to allow reversibility and avoid fatal outcome.

**Patient Description**

In September 1998, a 73 year old woman with a 1 week history of postprandial vomiting, progressive jaundice, dark urine and pruritus was admitted to our department. The patient denied any past history of jaundice, alcohol consumption or exposure to blood components. Her past history was unremarkable except for hypertension treated for over 2 years with enalolol 50 mg four times daily and nifedipine 10 mg twice daily. During the previous 14 months the patient had also been taking nitrofurantoin 100 mg four times a day as a prophylaxis against recurrent UTI and denied having any side effects.