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CASE REPORT

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Specific immunotherapy-induced Sjögren's syndrome

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Abstract *Background*: Allergen-specific immunotherapy (SIT) is a well-documented treatment for allergic rhinitis, asthma, and allergy to bee venoms. Side-effects of SIT in long-term have not been well documented yet. Herein, we report a case of Sjögren's syndrome following SIT. *Case*: The patient, a 25-year-old Caucasian woman, was started on subcutaneous grass-pollen immunotherapy. The patient's autoantibodies before the SIT screening tests were negative. We determined that anti-extractable nuclear antigen (ENA) was positive (ENA = 98.4, normal range 0–25 U) on routine screening tests at 44 weeks of her treatment, and then SIT was discontinued. The patient complained of burning and itching in her eyes for 6 months. Schirmer's and salivary flow tests were positive. Although antinuclear antigen and rheumatoid factor were negative, anti-SS-A/Ro was positive. Viral hepatitis markers were negative. Minor salivary-gland biopsy was performed, which showed grade 4 sialoadenitis. The HLA type of the patient was B55 (B22), Bw6, Cw1 for class I and DR11, DR52, DQ7 (DQ3) for class II. After the immunotherapy had been stopped, there were no changes in the symptoms and laboratory findings of the patient during the 1st year of follow-up. *Conclusion*: This is the first case to be reported of Sjögren's syndrome following SIT. Patients undergoing SIT must be carefully followed up for the development of autoimmunity and an autoimmune disease.

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Introduction

Primary Sjögren's syndrome (SS) is a systemic immune-mediated disease primarily characterized by chronic inflammation of the exocrine glands and clinical symptoms of dry eyes and dry mouth, although the systemic process may also involve additional organ systems [1]. Allergen-specific immunotherapy is a well-documented treatment for allergic rhinitis, asthma, and allergy to bee venoms [2]. As side effects due to specific immunotherapy (SIT) are local and systemic reactions in short term, the side effects in the long term are not yet known [3]. Herein, we report the case of a woman who developed primary SS due to subcutaneous grass-pollen SIT.

Case

In February 1998, the patient, a 25-year-old Caucasian woman, was started on clustered immunotherapy composed of subcutaneous grass pollen (ALK SQ, Hamburg, Germany). The SIT solution contained a number of allergens, identified by her skin test. The patient's autoantibodies (antinuclear antigen = ANA, rheumatoid factor = RF and anti-extractable nuclear antigen = anti-ENA) before SIT screening tests were negative. Grass-pollen SIT solution in gradually-increased doses (1 (10 U/mL), through a total of 19 injections, were administered. We determined that anti-ENA was positive (anti-ENA = 98.4, normal range 0–25 IU) on routine screening tests at 44 weeks of her treatment, and SIT was stopped. The patient complained of burning and itching in her eyes for 6 months. She thought these symptoms had occurred due to allergic conjunctivitis. The patient's foreign-body sense and burning complaints

in the eyes had increased in the most recent 3 months. She did not have arthritis, arthralgia or dry-mouth complaints. Unstimulated salivary flow test resulted in 0.5 mL in 15 min (< 1.5 mL/15 min), and Schirmer's test resulted in 5 mm in the right eye and 3 mm in the left eye in 5 min (< 5 mm/5 min). Leukopenia (2500 mm^{-3}) and lymphopenia (800 mm^{-3}) were found. Erythrocyte sedimentation rate, protein electrophoresis and plasma immunoglobulin levels were normal, and ANA and RF were negative. Plasma levels of immunoglobulin were normal except a slight increase in Ig A. Antibodies to Sjögren's syndrome-A antigen (SS-A/ Ro) were present, but antibodies to Sjögren's syndrome B antigen (SS-B/ La) were absent using the immunoblot technique. Antiphospholipid antibodies, cryoglobulins and autoantibodies to thyroid were negative. Other causes of dry eyes and dry mouth including viral infections (HIV, HTLV-I, hepatitis C and B), drugs and sarcoidosis in the patient were excluded. Labial salivary gland biopsy was performed, and two foci with more than 50 lymphocytes were observed in addition to scattered inflammatory cells (grade 4 by using criteria initially described by Chisholm and Mason and subsequently modified by Greenspan et al. to provide a quantitative scoring method) [4, 5] (Fig. 1). The HLA type of the patient was A24 and B55 for class I and DR11, DR52 and DQ7 for class II. Ten months after immunotherapy had been stopped, her common arthralgia symptom began. Hydroxychloroquine treatment was started the patient. After the cessation of the immunotherapy, there were no changes in the symptoms and laboratory findings of the patient during the 1st-year follow-up.

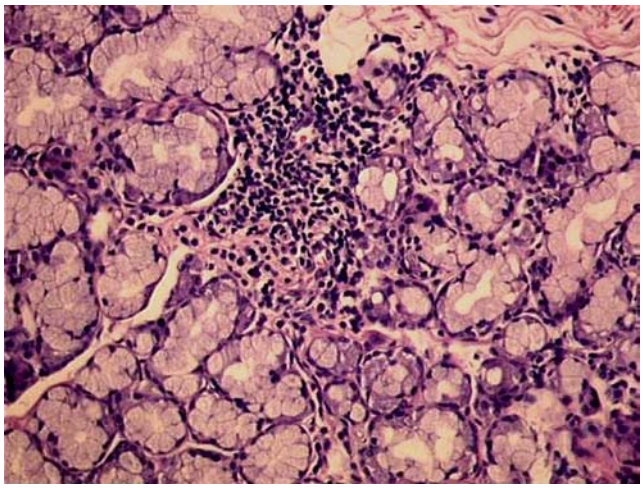

Fig. 1 A focus of lymphocytes and scattered inflammatory cells in the minor salivary gland biopsy specimen (Heamatoxylin-eosine 100 times)

Discussion

Primary SS is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, resulting most frequently in the symptoms of dry eyes and dry mouth. Infiltration of mononuclear cells embracing epithelial cells of the exocrine glands describes the main pathological process. Minor salivary gland biopsy is regarded a gold standard in the diagnosis of SS [1]. Our case had dry mouth and dry eyes and autoantibodies to SS-A/Ro. The diagnosis of SS was confirmed by the involvement of the salivary gland. The patient fulfilled the revised European classification criteria for SS [6].

The etiology of SS remains unknown, but the pathogenesis of exocrine cell damage is apparently multifactorial, including immunological, genetic, hormonal and viral components. Some evidence indicates that the true association of SS may be with HLA DQA1, which are linkage disequilibria with HLA DR3 and HLA DR5 in white patients [1]. Our patient had the DR11, DR52 and DQ7 genotypes. We could say she had a typical genetic background because she had HLA DR5 for SS.

Viruses are viable candidates, and indeed, some evidence suggest an involvement by retroviruses. Alternatively, this enhanced expression could be triggered by cytokines, such as interferon gamma. Autoimmune disease development related to immunotherapy was rarely reported. Toussirot et al. [7] reported the case of a woman who developed SS after the second dose of hepatitis B vaccine. Unoki et al. [8] reported the development of SS during treatment with recombinant human interferon-alpha-2b for chronic hepatitis C. In the literature, hydrallazine-induced SS has been reported, and it has also been shown that clinical parameters returned to normal after the discontinuation of hydrallazine therapy [9]. Our patient neither had viral infection nor used interferon therapy.

It is known that immunotherapy may cause the development of autoantibodies after a long-term antigenic stimulation. However, these autoantibodies vanish in 1 or 2 months after SIT is stopped. The development of SS in the patients to whom SIT was administered has not to date been recorded. In this case, SS might have developed because of chronic antigenic stimulation in an appropriate genetic background. For this reason, patients to whom SIT is administered must be carefully followed up for the development of autoimmunity and autoimmune disease.

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