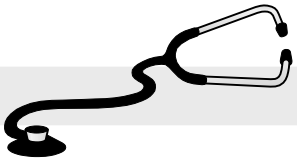

Multiple Autoimmune Disease in a Patient with Hyperprolactinemia

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The "mosaic of autoimmunity" 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.

Jaccoud's arthropathy is a clinical syndrome usually associated with systemic lupus erythematosus characterized by deformities with a rheumatoid arthritis-like clinical picture but no evidence of radiologic osteoarticular destruction or erosions. Urticarial vasculitis is a group of diseases characterized by urticarial lesions producing a burning sensation, persisting for more than 24 hours and resolving with purpura or hyperpigmentation. The disease may be categorized as normo or hypocomplementemic [1]. Urticarial vasculitis together with Jaccoud's arthropathy has been described rarely [2]. We describe such a case in a patient who, in addition, presented with SLE, Sjögren's syndrome and hyperprolactinemia, representing a classic example of the concept of autoimmunity developing as a mosaic.

Patient Description

A 28 year old woman visited our clinic (Corporacion para Investigaciones Biologicas) in May 1996 with a 4 year history of arthritis involving metacarpophalangeal joints, wrist, shoulders, and ankles. She also complained of galactorrhea that had begun a couple of months earlier. Her mother had an erosive rheumatoid arthritis and Hashimoto´s thyroiditis, and her grandmother had RA. Examination revealed synovitis with swelling in the metacarpophalangeal and proximal interphalangeal joints and ankles. She had an articular index of 12. Breast examination was normal. Extra-articular manifestations were absent. Blood tests showed mild anemia with hemoglobin 11.8 g/dl, erythrocyte sedimentation rate 81 mm/hour, C-reactive protein 96 mg/L and rheumatoid factor 3,072 IU/ml (by turbidimetry, positive >40 IU/ml) with normal white cell and platelet counts. Prolactin was 66.1 µg/ml (normal <20 ng/ml). Liver, renal and thyroid function tests were normal. X-rays of the hands showed no erosive changes. Computerized axial tomography of the sella turcica demonstrated a pituitary microadenoma. RA was suspected and therapy with methotrexate 7.5 mg a week, naproxen 500 mg twice a day and prednisone 10 mg per os daily was started. Later, the dose of methotrexate was increased to 10 mg a week and naproxen was switched to ketoprofen 200 mg twice daily. Cabergoline was prescribed for the patient's hyperprolactinemia.

In August of that year she complained of oral ulcers and pruriginous and painful hives on the skin of her extremities and abdomen, which persisted for 24 hours leaving dark macules. Initially, methotrexate and ketoprofen were stopped as they were believed to be the cause of the hives, but the urticarial rash persisted. A skin biopsy revealed perivascular neutrophilic infiltrates consistent with leukocytoclastic vasculitis. Laboratory workup disclosed a CH50 complement level of 6 IU/ml (normal 20–40 IU/ml), C3 was 45 µg/dl (normal 75–140 µg/dl), C4 67 µg/dl (normal 10–40 µg/dl) and C1q inhibitor 8 mg/dl (normal 7–24 mg/dl). Hypocomplementemic urticarial vasculitis was diagnosed and colchicine was administered, but there was no marked improvement in her condition.

The patient failed to attend her follow-up, but visited the clinic almost 6 years later in April 2002. During that period she had relapsing and recurrent urticarial rash and inflammatory pain of the hands and knees, and she developed a hallux valgus that required surgery. Sicca symptoms (mainly xerostomia) began to appear. When she returned to the clinic, she was found to have metacarpophalangeal subluxation, ulnar deviation, swan neck deformity of the fingers and Z deformity of both thumbs. X-rays of her hands and feet did not show any erosions or osteoarticular destruction but revealed multiple subluxations, a radiologic picture compatible with Jaccoud's arthropathy. A complete laboratory workup disclosed the following: hemoglobin 9.9 g/dl, normal white cell and platelet counts, ESR 101 mm/hr, rheumatoid factor 2,460 IU, immunoglobulin G anti-RNP antibodies 28.7 IU (normal <20 IU), IgG anti-SSA (Ro) antibodies 73.5 IU (normal <20 IU), IgG anti-SSB (La) antibodies 117.7 IU (normal <20 IU), C3 38.8 mg/dl, C4 10 mg/dl; anti-

SLE = systemic lupus erythematosus

RA = rheumatoid arthritis

ESR = erythrocyte sedimentation rate
IgG = immunoglobulin G

Sm antibodies were negative and anti-ds DNA antibodies were positive. HLA class II typing disclosed DRB1*0301 QDB1*0201 alleles. An echocardiography revealed mild thickening and prolapse of the mitral valve. In summary, the patient had Jaccoud's arthropathy, hypocomplementemic urticarial vasculilis, SLE, secondary Sjögren's syndrome, and a previous history of prolactinoma; her mother and grandmother had RA.

Comment

Differentiation between lupus arthritis and RA sometimes can be difficult, especially if the patient with SLE initially has only articular manifestations without any other systemic compromise or specific autoantibodies (i.e., anti-DNA, anti-Sm, anti-CCP). Patients with lupus arthritis might present with chronic and recurrent inflammation leading to deformities. In RA, X-rays disclose joint erosions. Deformities in SLE are caused by loss of soft tissue support without erosions or cysts on X-ray, and are, at least initially, passively reversible. Wrist function is almost always normal. This reversible form of arthritis is termed Jaccoud's arthropathy although it is not exclusively seen in SLE.

Urticarial vasculitis is an uncommon autoimmune disease. Characteristic skin lesions are undifferentiated from those seen in allergic urticaria. However, in true urticaria, lesions are pruritic and persist for a maximum of 8 hours without residual lesions. In urticarial vasculilis, they are not pruritic but often painful. The vascular targets are dermal capillaries and postcapillary venules in the upper dermis. Urticarial vasculitis can be a primary or secondary disorder associated with an underlying disease. Secondary forms have been described in patients with SLE, monoclonal gammopathy, neoplasia, serum sickness, hepatitis C virus, and Sjögren's syndrome [1].

As in the case of Jaccoud's arthropathy, the most common disease associated with hypocomplementemic urticarial vasculilis is SLE, and some investigators proposed that the vasculitis may be a subset of SLE or an unusual type of SLE. In fact more than 95% of patients are positive for anti-DNA or anti-Sm [1]. The association of Jaccoud's arthropathy and hypocomplementemic urticarial vasculitis is rare, with only six cases reported in the literature [Table].

Table 1. Hypocomplementemic UV and Jaccoud's arthropathy – Review of literature

Case	ANA/ DNA	ENA	C3/C4	CH50	C1q inhibitor	Other findings
1 J *Rheumatol* 1988;15:858–61	–/–	–	Low/Low	Low	Normal	Right profound femoral and renal artery stenosis. Medium-sized muscular artery vasculitis of the gall bladder associated with abdominal pain. Mitral and aortic regurgitation
2 J *Allergy Clin Immunol* 2000;106:1196–8	–/–	–	Low/Low	Low	High	Tricuspid regurgitation Mitral and aortic regurgitation
3 ref. 2	–/–	–	Low/Low	Low	Normal	Mitral stenosis Abdominal pain Mitral and aortic regurgitation
4 ref. 2	–/–	–	Low/Low	Low	Normal	Ocular inflammation Tracheal stenosis Abdominal pain Mitral and aortic regurgitation
5 ref. 2	-/-	–	Low/Low	Low	Normal	Ocular inflammation Abdominal pain Mitral and aortic regurgitation
6 J *Rheumatol* 2001;28:383–6	–/–	–	Low/Low	Low	ND	Mitral stenosis Tricuspid regurgitation Tracheal stenosis. Prolactinoma
7 Present case	+/+	Ro, La, RNP	Low/Low	Low	Normal	SLE Sjögren's syndrome Mitral valve thickening and prolapse

ND = no data, ANA = antinuclear antibodies, ENAS = extractable nuclear antigen antibodies.

Alarcon-Segovia et al. [3] pointed out that patients with Jaccoud's arthropathy and SLE have a higher incidence of Sjögren's syndrome, anti-ds DNA antibodies and positive rheumatoid factor than patients without it. They also may have a lower incidence of malar rash, rheumatoid nodules and photosensitivity [3]. Characteristically, our patient also had those features. In addition, she had hyperprolactinoma, which has been associated with SLE [4]. Circulating prolactin is elevated in about 20% of SLE patients and acts as an immunomodulator involved in lymphocyte survival, activation and proliferation [4], and could be the trigger for the multiple autoimmune diseases observed in our patient, who in addition carried the haplotype HLA-DRB1*0301-DQB1*0201 which has been characteristically associated with SLE.

The clustering of more than one autoimmune disease is a well-known phenomenon [5]. In the patient described here it would seem that the combination of genetic susceptibility, female gender and hyperprolactinemia constitutes the pieces of the mosaic that presented with the development of an assortment of autoantibodies and multiple autoimmune diseases.

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