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CASE REPORT

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A case of systemic lupus erythematosus: continued association of circulating prolactin levels with disease activity over a 4-year follow-up period

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Abstract Circulating prolactin levels in a woman with systemic lupus erythematosus (SLE) were measured over a period of 4 years, and her hyperprolactinemia remained associated with disease activity throughout. Circulating prolactin could thus be a better practical marker than standard parameters such as anti-double-stranded DNA antibodies and serum complement in some patients with SLE.

Key words Long-term follow-up · Prolactin · Systemic lupus erythematosus (SLE) · Systemic lupus erythematosus disease activity index (SLEDAI)

Introduction

The serum titer of anti-double-stranded (ds) DNA antibodies, the levels of serum complements and proteinuria, and degree of urine casts reflect the disease activity of systemic lupus erythematosus (SLE). However, because some patients with central nervous system symptoms often show discrepancies between the results for these parameters and disease activity, a better clinical indicator is needed. Over the past decade, hyperprolactinemia (HPRL) has been found in 20%–30% of patients with SLE,[1] and accumulating evidence has supported the hypothesis that elevated serum prolactin (PRL) may participate in the clinical expression and pathogenesis of the disease.[2] However, there are few reports of circulating PRL level applied to evaluate disease activity. We herein report a patient with SLE whose circulating RPL was regularly measured over 4 years and demonstrated a good correlation in its fluctuation with the systemic lupus erythematosus disease activity index (SLEDAI) score. Prolactin, a versatile hormone with more than 300 separate functions, is produced in the anterior pituitary gland and affects mammary growth and differentiation. Its secretion is mediated via the dopaminergic pathway. It is now recognized that PRL is a cytokine and is produced in a number of extrapituitary sites, including neurons, prostate, decidua, mammary epithelium, endothelial cells, epidermal cells, and immune cells. Prolactin is important for maintaining immune competence, and plays an important role in animal and human immune responses.[3,4]

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Case report

The subject was a 35-year-old woman, diagnosed with SLE at the age of 14 years, with symptoms of fatigue, arthralgia, arthritis, leukopenia, lymphopenia, a positive fluorescent antinuclear antibody test (1:2560), positive results for lupus anticoagulant, and antibodies against double-stranded DNA (ds-DNA) and anti-β2-glycoprotein I. Anti-ds-DNA antibodies and anti-β2 glycoprotein I antibodies were detected by a MESCUP anti-ds-DNA enzyme-linked immunosorbent assay (ELISA) kit (MBL, Nagoya, Japan) and a MESCUP anti-β2 glycoprotein I ELISA Kit (MBL), respectively. Lupus nephritis type IV was diagnosed by kidney biopsy at the age of 23, and the disease ameliorated to a state of remission with two courses of steroid pulse therapy. She became pregnant when 26 years old, but aborted because of intrauterine fetal death due to thrombosis in the placenta. Nephritis flared up again at the age of 28, and the patient received ministeroid pulse therapy of methylprednisolone 500 mg/day for 3 days. A third episode of nephritis occurred at the age of 29, which required six courses of steroid pulse therapy and three courses of intravenous cyclophosphamide pulse therapy of 500 mg/day per 3 weeks. On reappearance of nephritis when the patient was 30 years old, the disease was rediagnosed as type V in addition to type IV on the basis of kidney biopsy results. Nephritis improved with six courses of cyclophosphamide pulse therapy and three courses of plasmapheresis.

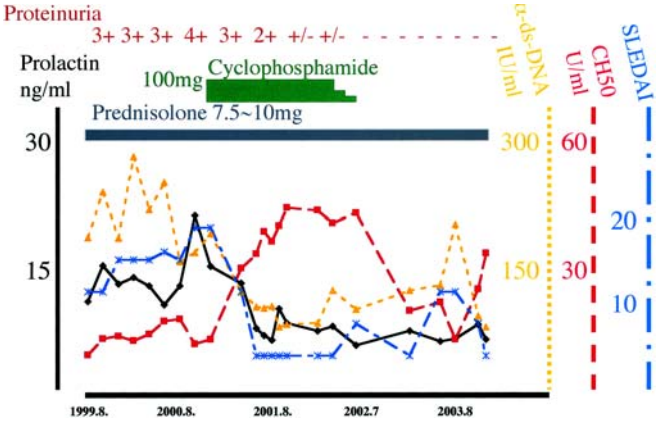

Fig. 1. Clinical course. Normal ranges for prolactin, α-double-stranded DNA (*α-ds-DNA*), and complement activity (CH_{50}) are 1.5–15 ng/ml, >12 IU/ml, and 30–45 U/ml, respectively. *SLEDAI*, systemic lupus erythematosus disease activity index

After intensive therapy at the age of 30, the circulating PRL in the patient has been measured periodically, given the reported good correlation between HPRL and the SLEDAI score.[5] Prolactin was measured by a SPAC-S Prolactin Kit (TFB, Tokyo, Japan). The patient has taken no medication affecting the secretion of PRL, and the presence of a pituitary tumor was excluded because the circulating PRL level was 21.5 ng/ml at most in 4 years, much lower than would be expected with such a neoplasm. After discharge from the last hospitalization, the patient has been followed up with administration of 7.5–10 mg prednisolone. In October 2000 The SLEDAI score was estimated at 20, showing a severe bout of lupus, but the patient's condition improved gradually with 100 mg of oral cyclophosphamide in addition to the prednisolone therapy. The titers of anti-ds-DNA, the amounts of serum complement, and the circulating PRL level changed in good concordance with the SLEDAI score (see Fig. 1). After cyclophosphamide was tapered off in August 2002, the titers of anti-ds-DNA again increased with a decrease in the serum complement in July 2003, whereas the SLEDAI score was at most 12 points in the range of moderate lupus during that period, and finally became 4 points without any therapy other than 10 mg prednisolone. The circulating PRL levels remained low.

Discussion

Our patient has suffered four relapses with nephritis that required strong immunosuppressive therapy or plasmapheresis and her circulating PRL has now been measured for 4 years after the last admission, and has shown a good correlation with SLEDAI in this period. There were small discrepancies in mid 2003 since the SLEDAI score became 12, while PRL removed normal. The increased SLEDAI score was due to pyruria 5–8 per high-power field (HPF) and hematuria 5–8/HPF. Anti-ds-DNA antibodies increased and serum complement decreased so that we anticipated deterioration, but in fact the SLEDAI score came down to 4 without any additional therapy. Retrospectively, PRL was thus more reliable than anti-ds-DNA antibodies or serum complement in predicting future disease activity of lupus during the period.

Hyperprolactinemia has been reported in SLE patients (20%–30%); however, the association with disease activity is controversial. Some discrepant findings may be explained by various factors such as the statistical power of the studies, variability in the groups of patients, and the SLE activity indices used, as well as anti-PRL antibodies.[2] However, new evidence has now accumulated of a significant relationship between serum PRL levels and SLE disease activity, especially in relation to lupus nephritis and the central nervous system, and cutaneous and articular manifestations.[6–8] Patients with active SLE have increased production of PRL with different molecular weights of 11 and 60 kDa.[9,10] A recent study has clarified that there are immunoreactive PRLs of 130 and 23 kDa and that the concentration of the 130-kDa species is 10-fold higher in patients with inactive SLE than in their counterparts with active disease.[11] The association between HPRL and high levels of interleukin-6 in both lupus nephritis and neuropsychiatric lupus suggests a bidirectional communication between the immune and neuroendocrine systems in SLE.[2]

High levels of circulating PRL are known to stimulate immune responses in mice. When HPRL was induced in C57BL/6 female mice either by implanting syngeneic pituitary glands or by injecting exogenous mouse PRL, primary humoral antibodies were increased in response to sheep red blood cells.[12] In another study, mice injected with 100 or 200 μg of bovine PRL demonstrated increased production of antisheep red blood cell antibodies, but no effects after a 400-μg dose.[13] Prolactin is recognized as a potent stimulator of macrophages,[14] increasing the production of macrophage interleukin-1 and nitric oxide[15] and stimulating phagocytic activity in mice.[16] Physiologic doses of PRL also cause macrophages to produce interferon-γ in humans,[17] although HPRL is itself associated with tissue depletion of macrophages. When cycling rats were treated with the PRL-suppressive agent CB154, the serum PRL concentrations were lowered significantly and the numbers of macrophages were reduced in regressing corpora lutea.[18] Therefore, further efforts to clarify the relationship between regulation of macrophage function in response to PRL and the pathogenesis of SLE are warranted.

To our knowledge, this report documents data from the longest period of measurement of circulating PRL in a patient with SLE, the results indicating that levels of PRL reflect disease activity. We propose that circulating PRL be considered as an alternative parameter for estimating the extent of disease activity in selected patients with SLE.

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