

## Case Report

### Exacerbation of lupus nephritis in association with leuporelin injection for uterine leiomyoma

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#### Introduction

Systemic lupus erythematosus is recognized as being influenced by oestrogenic hormones. Flares in disease activity have been described following hormonal manipulation to induce ovulation in fertility treatment [1]. The mechanism is said to be via surges in oestrogen levels.

Leuporelin (leuprolide acetate) is a gonadotrophin-releasing hormone analogue used to treat a wide variety of sex-hormone-related disorders including prostatic carcinoma, endometriosis, and uterine leiomyomata. Initial administration of leuporelin is associated with a marked increase in serum FSH and LH associated with corresponding rise in oestrogen. With prolonged administration, however, receptor desensitization occurs, resulting in postmenopausal oestrogen levels [2]. This occurs after 2 weeks of administration and gonadotrophin, and therefore sex hormone levels remain suppressed thereafter for the duration of treatment.

Uterine leiomyomata are oestrogen-sensitive tumours. Treatment with leuporelin results in decreased uterine volume and symptomatic improvement from menorrhagia [3].

#### Case report

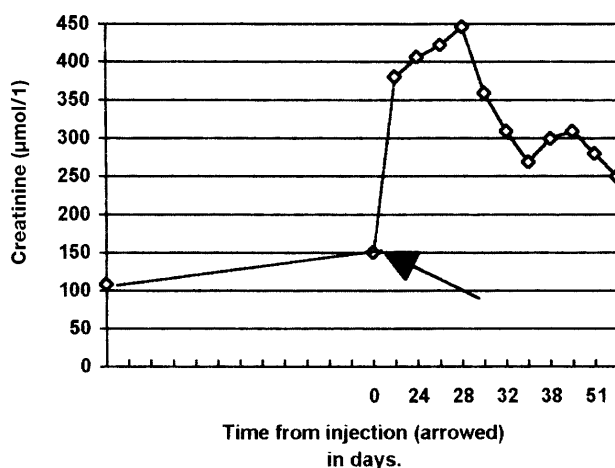
A 37-year-old with mild renal impairment due to lupus nephritis had been followed up by our unit for 10 years. A renal biopsy in 1986 showed mesangial proliferation and hypercellularity, but with no crescent formation, the appearances corresponding to WHO class IV with activity index 7/24 and chronicity 0/12. The patient was treated with pulse cyclophosphamide and oral steroid at that time. Over the following 10 years she has had recurrent flares of her disease involving joints, skin, and scleritis. She was treated consistently with hydroxychloroquine and prednisolone, her steroid dosage having been consistently below 10 mg since 1994. However, renal function had remained

stable with serum creatinine of approximately 100  $\mu\text{mol/l}$  and creatinine clearance of 65 ml/min, urinary 24-h albumin excretion in September 1996 was 0.9 g.

In early December of 1996 whilst maintained on 6 mg daily of prednisolone along with 200 mg hydroxychloroquine, the patient was admitted to another hospital with a markedly swollen leg. Venography and Doppler ultrasound excluded venous thrombosis, but bilateral early hydronephrosis was noted, thought to be due to compression by a large uterine fibroid. Serum creatinine had risen slightly to 155  $\mu\text{mol/l}$ .

It was decided to treat her fibroid medically in an attempt to shrink it in size prior to surgical removal, if still necessary following treatment. She was therefore commenced on a course of leuporelin 3.75 mg subcutaneously monthly.

Three weeks after the first dosage of leuporelin acetate the patient presented with malaise, arthralgia, myalgia, and orthopnoea. She was found to be hypertensive (180/125 mmHg) with a creatinine of 376  $\mu\text{mol/l}$  (Figure 1) and creatinine clearance of 11 ml/min. Urinary albumin excretion had increased to 4.6 g/24 h. She had a florid facial telangiectatic rash and pulmonary oedema. ANA titre was positive at



**Fig. 1.** Change in creatinine with time from injection of leuporelin acetate.

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1:2560, anti-nDNA at 1292 IU/ml, with low C4 and raised c3d.

Renal biopsy was repeated and showed a diffuse active crescentic and necrotizing glomerulonephritis in keeping with WHO class IV diffuse proliferative lupus nephritis with activity index 18/24 and chronicity 6/12. In addition the small arteries and arterioles showed severe fibrinoid damage.

Immunosuppression with oral cyclophosphamide and prednisolone was commenced. Two months after the initial injection, the patient's creatinine has fallen to 250 µmol/l and anti-nDNA to 328 IU/ml. The patient remains on immunosuppression and quadruple antihypertensive medication.

## Discussion

The most frequently reported side-effects of leuporelin are those associated with the hypoestrogenic state [4]. Adverse effects associated with the initial gonadotrophin surge have been reported in the literature however, including flares of endometriosis [5] and pituitary apoplexy [6].

In this case it appears that the oestrogen surge associated with commencing leuporelin treatment has precipitated an acute flare of lupus, associated with severe renal changes and causing renal failure. The close time association between the initial injection and onset of symptoms (2–3 weeks) is very strong circumstantial evidence, bearing in mind that the patient's disease had been quiescent for such a long period of time prior to receiving the treatment.

As far as we are aware this is the first reported case of increased lupus nephritis activity associated with administration of a gonadotrophin-releasing hormone analogue. Even with retrospective knowledge of the catastrophic effect that leuporelin treatment has had on this woman's disease activity and probable renal prognosis, the choice of treatment for her uterine leiomyoma was not easy. She had already begun to

develop significant renal outflow tract obstruction, which was the initial cause of deterioration in renal function. She is as yet nulliparous, would like to have children in the future, and surgical removal of a large fibroid would weaken the uterus for childbirth.

Activity index on renal biopsy has been shown to be the single most reliable factor in predicting renal outcome from lupus nephritis [7,8]. Our patient's future with regard to requirement for renal replacement therapy would therefore seem to be far less secure than prior to treatment for her leiomyoma.

We would recommend caution in considering hormonal manipulation in such patients in this manner. A possible precaution would be the concurrent use of an anti-oestrogen such as danazol in the initial treatment period [5].

## References

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