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Tubular Proteinuria during Treatment with Cyclosporin A—a Case Report

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ABSTRACT

A patient with relapsing polychondritis developed a progressive destruction of tracheal cartilage despite treatment with immunosuppressive and cytotoxic agents. Cyclosporin A therapy was instituted and has been continued for more than two years, concomitant with a steady improvement and remission of the disease. During the treatment period an increased urinary excretion of β_2-microglobulin was measured, indicating renal tubular damage. The tubular proteinuria preceeded an elevation of serum creatinine and a drop in creatinine-clearance. Thus, β_2-microglobulin might be a sensitive indicator of nephrotoxicity and of value for the evaluation of the long-term side effects of Cyclosporin A particularly in patients with extrarenal disease.

INTRODUCTION

Cyclosporin A (CyA) is a new potent immunosuppressive agent that is being increasingly used. One untoward effect of CyA is nephrotoxicity, with minor impairment of renal function up to severe acute renal failure (5, 6, 7).

This unfortunate side effect has complicated the therapy and raises questions as to the future widespread use of the drug. We here present the successful treatment with CyA in a patient with relapsing polychondritis, an uncommon autoimmune disorder (8). Measurements of β_2-microglobulin in serum and urine were used as an adjunct for the monitoring of the nephrotoxicity and the kidney damage.

METHODS

Cyclosporin A determination:

CyA plasma levels were determined using the radioimmunoassay (RIA) kit provided by the Sandoz Inc which detects concentrations of 50 to 2 000 ng/ml (3). The samples were taken in the morning as predose values, approximately 12 hours after the previous dose. The blood was drawn into heparinized vacuum tubes (Venoject®) and kept at room temperature (24°C) for at least one hour before centrifugation.

β_2-microglobulin

Serum samples were stored at -20°C until analysis. The urine sample was cooly stored, and a pH ≧6 ascertained by pH-strips. The concentration of β_2-microglobulin in serum and urine was determined by the Phadebas® β_2-micro Test (Pharmacia, Sweden).

Creatinine

Serum creatinine and the creatinine clearance (ml/min/ 1.73 m^2) was determined by an Autoanalyser technique at the Department of Clinical Chemistry, University Hospital, Uppsala.

CASE REPORT

A 52 year old woman was referred to our hospital in November 1980 with the clinical diagnosis of relapsing polychondritis. Her symptoms were swelling and erythema of the nose and ears, hoarseness, tenderness over the larynx and upper trachea, arthritis of peripheral joints and conjunctivitis. She had been treated with corticosteroids and Dapsone, both drugs giving pronounced side effects.

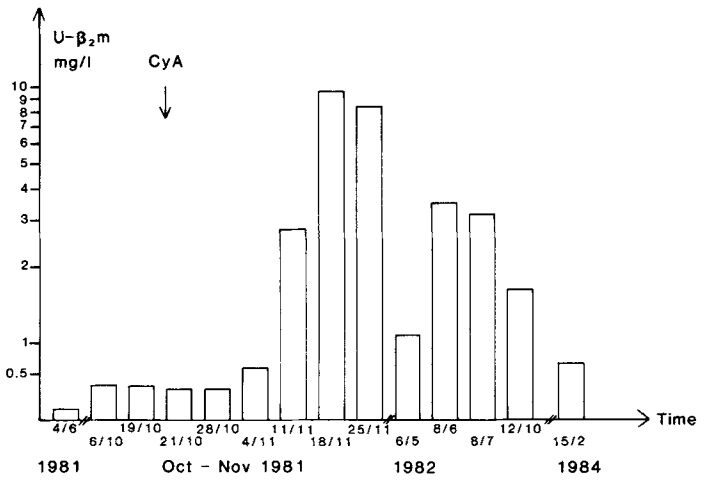
During the following months attempts were made to control the disease by Prednisolone (20-30 mg daily) together with azathioprine (2-3 mg/kg bwt) However, the illness steadily progressed with keratoconjunctivitis, increasing hoarseness, respiratory distress with stridor and bronchospasm and she developed a saddle nose. In June 1981 the Prednisolone dose was increased to 40-60 mg daily and the therapy was changed from azathioprine to cyclophosphamide in a daily dose of 100-150 mg. The progressive symptoms were still not prevented and side effects of alopecia and hepatic dysfunction appeared and the cyclophosphamide was withdrawn. Also the corticosteroid side effects were now severe and the clinical situation became desperate. She had expiratory and inspiratory stridor and X-ray of the trachea revealed a generalized cartilage destruction with a 3 mm lumen from the larynx to the carina.

Therapy with CyA was started on October 21, 1981 in a daily dose of 15 mg/kg/day. After 3-4 weeks of CyA-treatment a significant tubular proteinuria was observed and ALAT-values increased. The CyA dose was decreased first to 9 and later to 2 mg/kg/day. The signs of hepatotoxicity had then resolved. The future maintenance dose of CyA, about 5 (4.0-5.8) mg was started in the middle of December 1981 and is still, March 1984, continued. After about two months of critical illness after the start of the CyA therapy, the patient showed rapid clinical improvement. X-ray of trachea showed a widening of the lumen to 7 mm and there were no signs of disease activity. The Prednisolone dose has been gradually reduced to 5 mg Prednisolone on alternate days. At present, March 1984, she is in a good general condition, although an impairment of her renal function has developed.

RESULTS

Serum levels of CyA in November 1981, when the daily dose was 15 mg/kg, were found to be high, 1230 ng/ml. As the therapeutic level was thought to be in the range 100-400 ng/ml the dose was accordingly reduced, not least as signs of toxicity were simultaneously present. Later during the course of disease, at a dose of about 5 mg/kg, the serum level has been between 70 and 200 ng/ml.

The urinary excretion of β_2-microglobulin before CyA treatment, at weekly intervals in October-November 1981 when treatment was initiated, at four occasions in 1982 and now, 1984, is shown in the Figure at a logarithmic scale.



In the absence of renal insufficiency, U-β_2-microglobulin concentrations more than 0.5 µg/ml may be considered pathological and values more than 2.0 µg/ml indicate pronounced tubular proteinuria. In this case unequivocal tubular proteinuria was observed 3 weeks after the initiation of high dose CyA treatment. During the following year, at a lower dose of CyA but with therapeutic CyA serum levels, tubular proteinuria was still present but tended to diminish.

Before start of treatment, Oct 7th-21st, S-creatinine was 59-70 µmol/l, creatinine clearance 70 ml/min and S-β_2-microglobulin 1.2-1.4 mmol/l. All other S-creatinine values October 1981 - October 1982 were of the same size. Creatinine clearance, always measured when U-β_2-microglobulin was measured, only varied within the error of methods and seven out of nine determinations were in the range 48-54 ml/min. After the occurrence of tubular proteinuria in mid-November 1981 the S-β_2-microglobulin values increased from previous levels of 1.2-1.5 mg/l (n=4) to 2.1-2.7 mg/l (n=5, one deviating value of 1.5 mg/l in May 1982).

Now, in 1984 the S-creatinine level has slowly increased since the end of 1982 and is about 100 µmol/l with a creatinine clearance of 35 ml/min. Simultaneously the S-β_2-microglobulin level has increased to 4.5 mg/l.

DISCUSSION

The case, discussed in this report, has previously been described in detail (12) with respect to diagnostic and immunopathological aspects of relapsing polychondritis (RP).

High titers of circulating IgG anticollagen type II antibodies were found and immunohistochemical studies on affected cartilage suggested that macrophage-T-cell interaction might play an important role in the disease process. As CyA is believed to exert a specific effect on T-lymphocyte activation by inhibition of T-cell-macrophage interaction (6) it was a logical decision to chose CyA for an attempt to arrest the disease when other more conventional efforts had failed and life-threatening symptoms had developed.

Potential renal toxicity from CyA; glomerular, vascular, tubular and interstitial alterations (4, 5, 9, 10, 11), have been described in transplant recipients as well as in animal experiments after treatment with CyA. Hence, monitoring of renal function is mandatory during CyA treatment.

In this case the decision to reduce the dose of CyA was based on signs of tubular renal damage together with evidence of hepatotoxicity and the CyA serum levels. However, the role of plasma or blood CyA analysis in reaching a final "safety" dose of CyA is by no means clear. Proximal tubular dysfunction leads to an increased urinary concentration of β_2-microglobulin (2, 13).

The serum level of β_2-microglobulin is determined by the glomerular filtration rate and the rate of synthesis (1). Urinary β_2-microglobulin is a sensitive indicator of proximal tubular damage as the protein is normally reabsorbed to a higher extent than 99.9 %. In this case a 10-20 fold increase of the urinary excretion occurred after 3-4 weeks of therapy. During the following year an increased excretion persisted but the magnitude had decreased. Considering the experience that a tubular proteinuria, after acute tubular necrosis or in connection with a rejection crisis after kidney transplantation is usually a transitory event disappearing after weeks or months, one should retrospectively have suspected that a toxic injury was still going on during the continued therapy even at the lower dose. Possibly a slow process of fibrosis and sclerosis of glomeruli takes place if a nephron loss is initiated by injured tubules.

At an early stage of renal damage serum creatinine is an insensitive measure of a reduced GFR. Not least as in this case in the presence of muscular wasting, it is not surprising that S-β_2-microglobulin seemed to be a somewhat better indicator of a change in renal function (1). Not until after about 1½ year the decreased glomerular filtration was obtained through the use of determinations of serum creatinine. At that time, but not before, general proteinuria, with an excretion of about 100 mg of albumin daily, was detectable.

As in this case it sometimes turns out necessary to continue treatment with a toxic drug in spite of the fear for toxic sequelae. Still, the late occurrence of a reduced GFR was an unexpected development in the present case. As it was heralded by a long period of tubular proteinuria, we suggest that measurements of β_2-microglobulin, or other markers for tubular proteinuria, should be included as a routine in the management of CyA treated patients.

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REFERENCES

1. Berggård, J., Bearn, A.G.: Isolation and properties of a low molecular weight β_2-microglobulin occurring in human biological fluids. J Biol Chem 243:4095,1968.
2. Butler, E.H., Flynn, F.V.: The proteinuria of renal tubular disorders. Lancet ii:978,1958.
3. Donatsch, P., Abisch, E., Homberger, M., Traber, R., Trapp, M., Voges, R.: A radioimmunoassay to measure Cyclosporin A in plasma and serum samples. J Immunoassay 2:19,1981.

4. Hamilton, D.V., Calne, R.Y., Evans, D.B., et al.: The effect of long-term Cyclosporin A on renal function. Letter. Lancet 1:1218-1219,1981.
5. Hamilton, D.V., Evans, D.V., Thirus. In: Cyclosporin A, White DJG (ed), pp 393-411, Elsevier Biomedical, Amsterdam, 1982.
6. Keown, P.A., Stille, C.R., Ulan, R.A., et al.: Immunological and pharmacological monitoring in the clinical use of Cyclosporin A. Lancet I: 686-9,1981.
7. Marbet, U., Graf, U., Mimatsch, M.J., et al.: Renale Nebenwirkungen der Therapie mit Cyclosporin A bei Chronischer Polyarthritis und nach Knochenmark trasnplantation. Schweiz Med Wschr 110:2017-2020,1980.
8. McAdam, L., O'Hanlan, M., Bluestone, R., Pearson, C.: Relapsing polychondritis: Prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 55:193-215,1976.
9. Spichtin, H.P., Mihatsch, M.J., Oberholzer., et al.: Prognosis of kidney transplants by means of renal biopsy. Nieren und Hockdruckskrankheiten 3:95-100,1982.
10. Ryffel, B. In: Cyclosporin A, White DJG (ed), pp 45-76, Elsevier Biomedical, Amsterdam, 1982.
11. Shulman, H., Striker, G., Deeg, H.J., et al.: Nephrotoxicity of Cyclosporin A after allogenic marrow transplantation: Glomerular thromboses and tubular injury. N Engl J Med 305:1392-1395,1981.
12. Svenson, K.L.G., Holmdahl, R., Wibell, L., Klareskog, L., et al.: Cyclosporin A treatment in a case of Relapsing Polychondritis. Scand J Rheumatol. In Press.
13. Wibell, L., Evrin, P.E., Berggård, J.: Serum β_2-microglobulin in renal disease. Nephron 10:320-331,1973.