Idiopathic hypergammaglobulinaemia associated with nephrogenic diabetes insipidus and distal renal tubular acidosis

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Summary

Renal tubular dysfunction may be recognized in patients suffering from urinary light chain disease or non-myelomatous hypergammaglobulinaemia. We report a patient who has the combination of distal renal tubular acidosis and nephrogenic diabetes insipidus in association with hypergammaglobulinaemia due solely to increased IgG. We postulate that the abnormalities of distal nephron function resulted from cell-mediated immune damage.

KEY WORDS: bendrofluazide, nephritis, interstitial.

Introduction

Proximal and distal tubular dysfunction in myelomatous states is well documented and is universally associated with light chain proteinuria (Beaufils and Morel-Maroger, 1978). Tubular abnormalities are also seen in patients with increased urinary light chain excretion, in the absence of serum immunoglobulin abnormalities (Smithline *et al.*, 1976). In contrast, non-myelomatous hyperglobulinaemia can give rise to tubular anomalies, more often of the distal variety, in the absence of urinary light chains (McCurdy, Cornwell and Depratti, 1967). Although cases of distal renal tubular acidosis in association with hyperglobulinaemia of diverse origins have been reported (Mason and Golding, 1970), the combination of distal renal tubular acidosis and nephrogenic diabetes insipidus in non-myelomatous hyperglobulinaemia is uncommon.

We wish to report a patient with these abnormalities.

Case report

A 30-year-old woman presented in 1965 with a

scaly rash of the hands and legs. The erythrocyte sedimentation rate (ESR) was raised and although circulating antinuclear antibody was not detected, a clinical diagnosis of systemic lupus erythematosus was made. Prednisolone and chloroquine were given without effect. From 1974 onwards the ESR was consistently greater than 90 mm/hr, although she remained physically well with no recurrence of joint problems or rash. In 1978 she developed excessive thirst, polyuria and nocturia and during the following 4 years she was regularly drinking 9 litres of fluid daily. She had no other complaints. There was no evidence of chronic urinary tract infection, analgesic abuse or psychiatric disturbance. Physical examination was normal.

In hospital, polyuria was confirmed (urine output 6-7 litres/24 hr). Serum electrolytes showed mild hyperchloraemic acidosis—chloride 112 mmol/l, bicarbonate 20 mmol/l, creatinine 209 μ mol/l, and potassium was 3.7 mmol/l. Serum total protein was raised at 102 g/l, due entirely to an elevation of serum IgG to 39.5 g/l (normal 0.5-16.5 g/l), which was polyclonal on immuno-electrophoresis. The ESR was 116 mm/hr. Bone marrow aspiration revealed normal erythropoiesis and myelopoiesis. All auto-antibodies, including antinuclear factor and DNA binding activity, were negative. Serum complement levels were normal. Intravenous pyelography showed no abnormality.

Glomerulofiltration was slightly impaired (creatinine clearance 75 ml/min). Urinary protein excretion was less than 0.3 g/24 hr, and light chains were not detected. Screening tests for proximal tubular function were normal; there was no glycosuria (plasma glucose 4.9 mmol/l), urinary phosphate excretion was normal at 16.3 mmol/24 hr (plasma phosphate 0.86 mmol/l), as was urate excretion at 3.5 mmol/24 hr (plasma urate 0.52 mmol/l), and amino-acid chromatography of the urine was also normal.

However, distal tubular function was abnormal. Following an oral ammonium chloride load (0.1 g/kg) urinary pH did not fall below 6.21 (arterial blood pH 7.36). Urine osmolality under conditions of free access to fluid ranged from 99–178 mmol/kg, but after fluid deprivation for 14 hr, urine osmolality remained consistently low, of the order of 200–250 mmol/kg, despite the rise in plasma osmolality to 296 mmol/kg, and failed to increase after administration of 2 μ g desmopressin i.m. (Monson and Richards, 1978). Furthermore, urine osmolality was inappropriately low for the plasma vasopressin concentration measured by radioimmunoassay (Rooke and Baylis, 1982), which was persistently elevated (Fig. 1).

FIG. 1. The relationship of this patient's plasma vasopressin concentration to urine osmolality after overnight dehydration for 14 hr (●). The shaded area represents the normal relationship between urine osmolality and plasma vasopressin during dehydration and water loading.

Histological examination of a renal biopsy specimen revealed considerable tubular atrophy with heavy infiltration of plasma cells, lymphocytes, and moderate interstitial fibrosis, but no glomerulonephritis. Immunofluorescent studies failed to demonstrate gammaglobulin in association with the tubules and amyloid was not present.

She has subsequently been treated with bendrofluazide, 5 mg daily, which reduced her polyuria to 2.5 litres/24 hr and she remains otherwise well.

Discussion

Our patient demonstrated the unusual combination of a polyclonal gammopathy in association with distal renal tubular acidosis and a vasopressin resistant renal concentrating defect. Following an oral ammonium chloride load the minimum urinary pH achieved was 6.21 (urine pH is normally depressed to 5.2 or below), clearly indicating an acidifying defect. Her plasma bicarbonate ranged between 18 and 20 mmol/l under basal conditions, suggesting that the defect was mild. The remainder of her abnormal biochemistry was in keeping with renal

tubular acidosis showing a persistent mild hyperchloraemia and a low normal serum potassium. There has, to date, been no evidence of renal calcification.

Diabetes insipidus was unequivocally demonstrated by her low urine osmolality (250 mmol/kg) after a prolonged period of fluid deprivation (plasma osmolality 296 mmol/kg). Nephrogenic rather than cranial diabetes insipidus was indicated by her repeated failure to respond to desmopressin, and was confirmed by the plasma vasopressin concentration being inappropriately elevated in relation to urine osmolality (Fig. 1), in keeping with end-organ unresponsiveness. The absence of glycosuria, normal urinary phosphate and urate excretions, and urinary amino-acid chromatography, all indicated intact proximal tubular function.

Our failure to detect gammaglobulin deposited around the tubules is similar to one previously reported case of idiopathic hyperglobulinaemia with renal tubular acidosis and probable diabetes insipidus (McCurdy *et al.*, 1967). Renal biopsies performed in 10 patients with distal renal tubular acidosis and immunological abnormalities, but without nephrogenic diabetes insipidus, also showed no immune deposits (Feest *et al.*, 1978). We postulate that, in our patient, cell-mediated immune damage was responsible for her functional abnormalities, and the heavy cellular infiltrate observed in the renal biopsy would be consistent with this hypothesis.

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