Transient Suppression of Erythropoietin Synthesis in Hydronephrosis

Y.	Yoshito	Tsukada
N.	Naoya	Murata
S.	Shintaro	Yano
T.	Takuji	Naruse

Third Department of Internal Medicine, Gunma University School of Medicine, Maebashi, Japan

Dr. Y. Tsukada, Third Department of Internal Medicine, Gunma University School of Medicine, Showa-machi Maebashi, Gunma, 371 (Japan)

Dear Sir,

We report a case of hydronephrosis due to bladder neck contracture which resulted in renal failure and anemia. Urinary tract decompression resulted in the prompt reduction of the serum creatinine (Cr) level and restored erythropoietin (Epo) synthesis. Subsequently, the patient's profound anemia resolved. We conclude that hydronephrosis resulted in a transient suppression of Epo synthesis.

A 72-year-old woman was admitted to our hospital with rapidly deteriorating renal function and severe anemia. One month prior to admission, she had noted dysuria and pretibial edema. At that time, laboratory evaluation showed a serum Cr 3.0 mg/dl (363 $\mu\text{mol/l}$), BUN 34 mg/dl (5.5 mmol/l), and Hb 6.1 g/dl (61 g/l). Four weeks later, the serum Cr was 5.6 mg/dl (490 mmol/l) and she was transferred to our hospital with a diagnosis of acute renal failure.

The past medical history was remarkable for cervical cancer treated 23 years previously by uterine resection and pelvic irradiation. On examination, the patient was afebrile and pale. The pulse was regular at 64/min and the blood pressure was 156/70 mm Hg. The lungs, the heart, and abdomen were normal. The neurologic examination was normal. Pretibial edema was minimally present following diuresis at the previous hospital.

Initial laboratory data were as follows: serum Cr 7.9 mg/dl (691 mmol/l) BUN 105 mg/dl (17 mmol/l), UA 7.9 mg/dl (469 $\mu\text{mol/l}$), Hb 6.9 {kz} g/dl (69 g/l), Hct 20.8%, reticulocyte 0.3%, WBC 5×10^7 , platelets 154×10^7 , serum Fe 179 mg/dl (32.0 $\mu\text{mol/l}$), unsaturated iron binding capacity 16 mg/dl (2.86 $\mu\text{mol/l}$), ferritin 570 mg/dl (57 $\mu\text{g/l}$), plasma Epo 9.9 mU/ml (range 8-36) ESR 55 mm/h, CRP 0.4 mg/dl (4,000 $\mu\text{g/l}$). The

Fig. 1. Clinical course. Serum Epo was serially measured in the course of management. Normal levels were gradually achieved as serum Cr decreased.

urine showed 1.8 g protein/24 h, pH 5.0, granular and hyaline casts, glucosuria (1+), and an absence of hematuria and eosinophil-uria. Bilateral hydronephrosis and hydro-ureter were observed on renal ultrasonography with minor atrophy of the renal cortices. A profile of the renogram revealed a significant retardation of the excretion phase in both kidneys. Voiding cystourethrography on initial catheterization showed mild trabeculation and stenosis in the neck of the bladder. Vesi-coureteral reflux was not observed.

These findings along with subjective symptoms of impaired urination suggested that obstruction of the lower urinary tract resulted in renal failure. Bladder neck stenosis was confirmed by transurethral insertion of a metal bougie. The residual urine

Clinical Course

volume was more than 300 ml. Continuous bladder catheterization was started and after 5 weeks changed to intermittent self-catheterization. This strategy resulted in a marked improvement in renal function. After 3 weeks, distigmine bromide was begun and 1 week later prazosin hydrochloride was added to the regimen (fig. 1). Residual urine volumes fell below 100 ml 2 weeks after self-catheterization was initiated.

Serum Epo was serially measured in the course of management. Normal levels were gradually achieved and the hemoglobin correspondingly increased to 9.2 g/dl (92 g/l) by the time of discharge. Mild proteinuria, observed on admission, resolved completely. A percutaneous renal biopsy was performed on the 10th hospital day when the serum Cr

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was 1.6 mg/dl (140 mmol/l). Histologic examination revealed flattening of the proximal tubular epithelial cells, thickening of the tubular basement membrane, a mild interstitial fibrosis, and minor glomerular abnormalities (fig. 2). Two months after admission, the patient was discharged on a regimen of intermittent self-catheterization following spontaneous urination. During follow-up her serum Cr and her anemia resolved. Six months after discharge, the serum Cr was 0.9 mg/dl (78.8 mmol/l) and the hemoglobin was 11.8 g/dl (118 g/l).

The pathogenesis of an incomplete bilateral obstruction of the lower urinary tract is unclear. Bladder neck obstruction may have resulted from the pelvic irradiation administered 23 years ago. The resulting hydronephrosis and deterioration of renal function were reversed by relieving the bladder neck obstruction. The good early response to decompression corresponds with the minor glomerular abnormalities and mild interstitial changes demonstrated on renal biopsy.

Thus, it can be assumed that severe hydronephrosis was not long-standing.

The most intriguing aspect of this case was that resolution of the hydronephrosis was accompanied by spontaneous recovery from anemia. Initial laboratory findings indicated that the patient's anemia was due to decreased red cell production, probably due to a disorder of Epo synthesis. The reduction of Epo synthesis which occurred during the hydronephrotic state resolved with bladder decompression and serum Epo levels returned to normal.

Jacobson et al. [1] showed that rats made uremic by bilateral ureter ligation responded to blood loss with a near-normal Epo release. On the other hand, Jelkmann et al. [2] reported that 3 months of ureter ligation with

Fig. 2. Renal biopsy taken 5 weeks after catheterization. Flattening of the proximal tubular epithelial cells, thickening of the tubular basement membrane, and a mild interstitial fibrosis were present. The glomeruli have minor abnormalities.

the contralateral kidney removed resulted in low plasma Epo reactivity to hypoxia. These observations indicate that in uremia secondary to hydronephrosis, Epo synthesis is preserved in the early period. Several case reports of erythrocytosis associated with unilateral hydronephrosis and cured by decompression have been reported [3]. Polycythemia, in these cases, was presumably a consequence of increased synthesis and release of Epo. These cases and ours

demonstrate that disorders of Epo synthesis may result from hydronephrosis and that correction of the underlying obstruction relieves this problem. Recently, the precise region of Epo synthesis was reported to be the peritubular interstitial or endothelial cells by in situ hybridization [4,5]. Sustained high hydrostatic pressure in the renal tubules which indirectly increase interstitial pressures may have suppressed Epo synthesis in our case.

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While no clinical reports of coexisting hydronephrosis and anemia have been previously published, acute interstitial nephritis (AIN) complicated by anemia has been described [6,7]. In those cases, the prednisolone therapy of AIN resulted in rapid recovery of the hemoglobin level. The relationship of AIN and anemia has not been investigated in terms of suppression of Epo production. In addition to secondary anemia due to inflammation, infiltrating inflammatory cells in the interstitium may abrogate Epo synthesis.

To our knowledge, this is the first report of an obvious relationship between the improvement of hydronephrosis and the resolution of anemia. Serial assays of the serum Epo level over the course of the therapy corresponded to the initial profound anemia and its subsequent resolution. Whether alterations in Epo synthesis and/or release are common in hydronephrosis merits further analysis.

References

Jacobson LO, Goldwasser E, Fried W, Plazak L: Role of the kidney in erythropoiesis. *Nature* 1957;179:633-634.

Jelkmann W, Marienhoff N, Giesselmann S, Busch L: Lowered plasma erythropoietin in hypoxic rats with kidney tubule lesions. *Blut* 1988;57:317-321.

Jaworski ZF, Wolan CT: Hydronephrosis and polycythemia: A case of erythrocytosis relieved by decompression of unilateral hydronephrosis and cured by nephrectomy. *Am J Med* 1963;34:523-534.

Lacombe C, DaSilva J-L, Bruneval P, Fournier JG, Wendling F, Casadevall N, Varet B, Tambourin P: Peritubular cells are the site of erythropoietin synthesis in the murine hypotonic kidney. *J Clin Invest* 1988;81:620-630.

Koury ST, Bondurant MC, Koury MJ: Localization of erythropoietin synthesizing cells in murine kidneys by in situ hybridization. *Blood* 1988;71:524-527.

Greising J, Trachtman H, Gauthier B, Valder-rama E: Acute interstitial nephritis in adolescents and young adults. *Child Nephrol Urol* 1990;10:189-195.

Chan TM, Kung AWC, Chan KW, Lam KSL, Cheng IKP: Acute interstitial nephritis and idiopathic cranial diabetes insipidus. *Nephron* 1992;60:492-493.