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Case Report

Acute Tubulointerstitial Nephritis Following Intravenous Immunoglobulin Therapy in a Male Infant with Minimal-Change Nephrotic Syndrome

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Tanaka, H., Waga, S., Tateyama, T., Sugimoto, K., Kakizaki, Y. and Yokoyama, M. *Acute Tubulointerstitial Nephritis Following Intravenous Immunoglobulin Therapy in a Male Infant with Minimal-Change Nephrotic Syndrome.* Tohoku J. Exp. Med., 1999, **189** (2), 155-161 —— A boy aged 4 years with nephrotic syndrome (NS) was referred to our hospital because of the third relapse of NS. Hypogammaglobulinemia associated with massive proteinuria was observed at the presentation. Residual urinary tract infection required intravenous piperacillin and immunoglobulin therapy (IVIG). Soon after IVIG, he complained of high fever with chills, bilateral knee joint pain, dry cough and chest discomfort. Although he did not develop renal insufficiency, a transient increase in the urinary β_2-microglobulin and decrease in the serum complement hemolytic activity were observed. These clinical manifestations spontaneously ceased. A percutaneous renal biopsy for his NS performed 19 days after the episode of allergic rection revealed tubulointerstitial nephritis (TIN) with marked eosinophil infiltrates. Glomeruli showed minor glomerular abnormalities. Renal complications associated with IVIG treatment have been reported to date, however, acute TIN has rarely been seen. ———— acute tubulointerstitial nephritis; hypersensitivity reaction; intravenous immunoglobulin therapy; minimal-change nephrotic syndrome

Intravenous immunoglobulin therapy (IVIG) has been used for a variety of clinical disorders, such as idiopathic thrombocytopenic purpura (Imbach et al. 1981), neurologic disorders (Ellie et al. 1992), collagen diseases (Corvetta et al. 1989; Silverman et al. 1990) and Kawasaki disease (Fischer et al. 1996). Despite its widespread utilization, renal complications associated with IVIG remains relatively uncommon. It have been reported that two types of renal complica-

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tions: Acute renal failure (ARF) probably caused by hyperoncotic pressure (Ahsan et al. 1994, 1996; Pasatiempo et al. 1994; Poullin et al. 1995; Hansen-Schmidt et al. 1996; Cayco et al. 1997), and acute hypersensitivity nephritis (Ellie et al. 1992). However, acute hypersensitivity nephritis following IVIG is relatively rare in the current literature.

We encountered a boy with nephrotic syndrome (NS) who developed acute tubulointerstitial nephritis (TIN) following IVIG without containing sucrose. The interstitial lesion seen in the biopsy specimen, showing massive eosinophil infiltrates suggested that a possible hypersensitivity play a role in the pathogenesis of his TIN.

Case Report

A 4-year-old boy with a 6-month history of NS was hospitalized with the third relapse of NS. Although he had been a steroid-responder, proteinuria did not respond to 4-week course of daily prednisolone (1.5 mg/kg) therapy at the third relapse. Thus he was referred to our hospital.

On admission, his body temperature was 36.8°C and blood pressure was 132/60 mmHg. No skin or mucosal lesions were observed. His body weight was 20 kg, which was found to be 4 kg more than the weight without edema. Physical examination was unremarkable except for puffy face and peripheral edema. Urine analysis showed a specific gravity of 1.025, 24-hour protein excretion of 3.6 g and 6 red blood cell sediments per high-powered field. Urinary β_2-microglobulin (β_2-MG) at the presentation was 90 μg/liter (normal, <300). Laboratory studies revealed the following abnormal results: Erythrocytes sedimentation rate, 53 mm per hour; serum total protein, 40 g/liter; albumin, 21 g/liter; total cholesterol, 7.2 g/liter; and fibrinogen, 6 g/liter. Normal laboratory results included leukocyte count, hemoglobin concentration, hematocrit, thrombocyte count, sodium, pottasium, chloride, calcium, urea nitogen (9 mg/100 ml), creatinine (0.6 mg/100 ml) and uric acid. Immunological tests revealed the following values: Immunoglobulin G (IgG), 3.5 g/liter; IgA, 2.0 g/liter; IgM, 1.2 g/liter; IgE, 45 U/ml (normal range, 100–400); C_3, 1.9 g/liter (0.7–1.3); C_4, 0.4 g/liter (0.2–0.5) and hemolytic complement activity (CH_{50}), 42.0 U/ml (30–40). Anti-nuclear antibody was not detected.

After admission, the patient was treated with water and sodium restriction and daily administration of furosemide with human albumin infusion. Because of steroid-resistant, the prednisolone dosage decreased to 1.0 mg/kg per day. A routine urine culture revealed residual *Pseudomonas aeruginosa* infection. Persistent proteinuria resulted in decrease in the serum IgG concentration to 1.8 g/liter by hospital day 10. Although he did not show the manifestation of urinary tract infection, he was thought to be a compromised host.

Thus prophylactic intravenous piperacillin (PIPC) therapy (0.5 g/8 hours) accompanied with IVIG containing no sucrose (Veno I®, Yoshitomi Co., Tokyo)

was started from hospital day 11. Within an hour after the start of 2.5 g of IVIG, he complained of chills, bilateral knee joint pain and dry cough with discomfort in the chest. His blood pressure and urine output remained unchanged, however, body temperature rised to 39.8°C. No flushing or urticaria was seen on the examination. Then IVIG was discontinued and intravenous hydrcortisone was given. On the next day these clinical manifestations completely ceased, and he remained free from renal insufficiency.

Thereafter, he had no complaints except for steroid-resistant proteinuria. The infusion regimen of PIPC for residual urinary tract infection was repeated without adverse reaction. Although a rise in serum urea nitogen or creatine level did not occurred, urinary β_2-MG increased to 10 250 μg/liter and serum CH_{50} decreased to 17.3 U/ml by hospital day 26. These abnormal laboratory findings spontaneously subsided by hospital day 47. Intravenous methyl-prednisolone pulse therapy for his steroid-resitant NS was performed from hospital day 56, and which resulted in a gradual subsidence of proteinuria. A search for serum anti-IgA antibody was unremarkable. His clinical course is shown in Fig. 1.

A percutaneous renal biopsy was performed at hospital day 30. Portion of 20 glomeruli were seen by light microscopy of hematoxylin-eosin stained sections. The glomeruli showed minor glomerular abnormalities. No sclerotic glomerulus was observed in the specimen. A large region of the interstitium showed infiltrates of mononuclear cells with prominent eosinophils (Figs. 2a and b). The

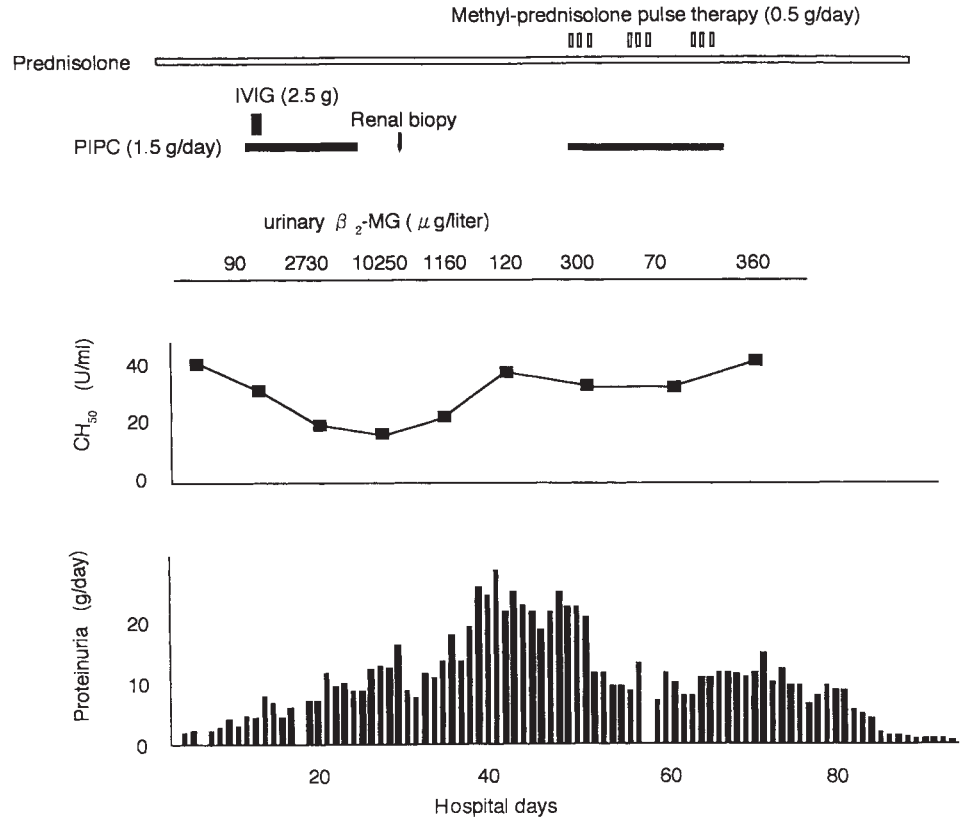

Fig. 1. Clinical course of the patient.

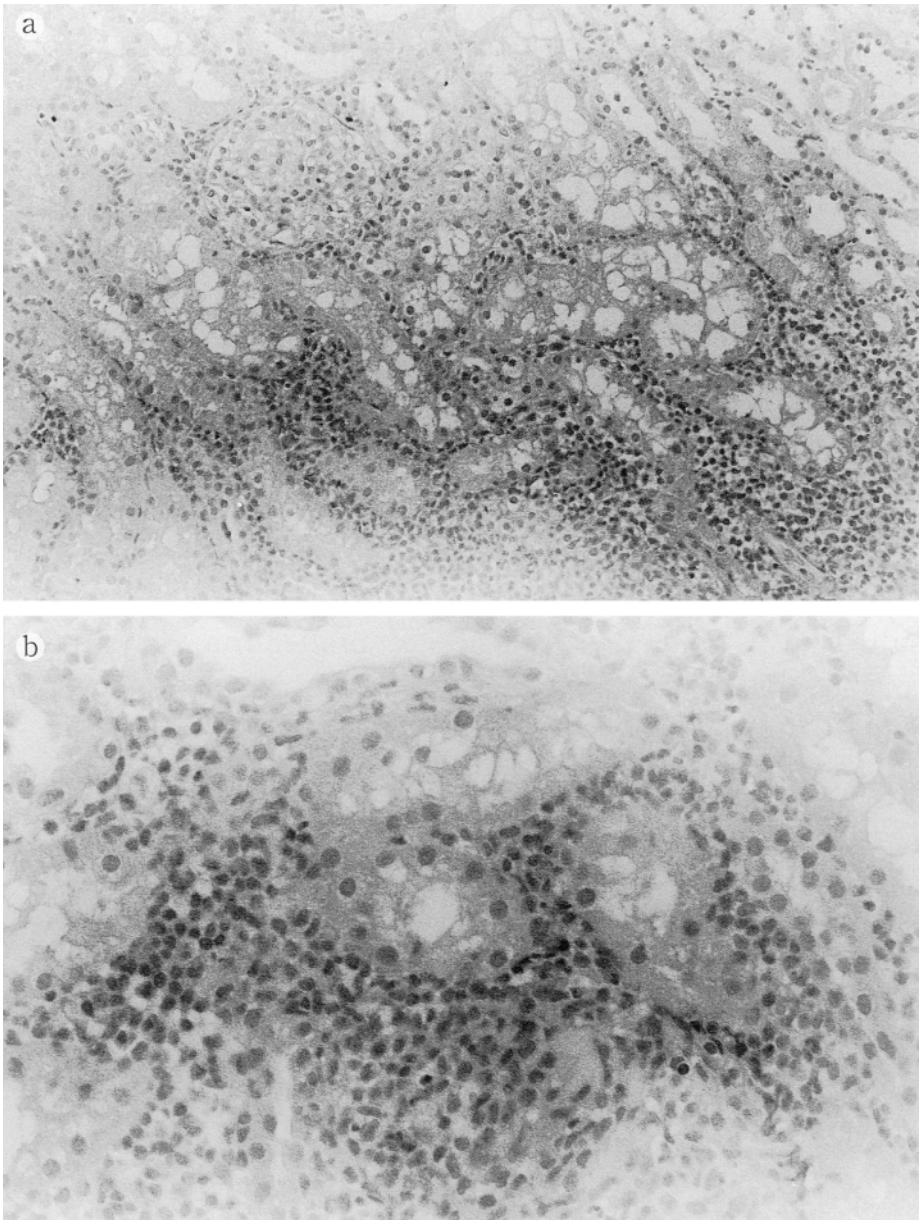

Fig. 2. Photomicrograph of interstitium from the patient demonstrating mononuclear cells with prominent eosinophils infiltrates. Glomeruli showed minor glomerular abnormalities (a: H & E staining, ×100). Tubular cell swelling and vacuolization are also seen (b: H & E staining, ×200).

moderate degree of proximal tubular cell swelling and vacuolization were observed. There were no vascular changes to suggest underlying systemic vasculitis. By immunofluorescence studies, 1+ of IgM and C_3 and a trace of C_4 were visible at glomerular mesangium. IgG, IgA and C_5 were not present in the specimen. Immunohistochemical studies for the interstitial infiltrate cells were not performed.

Discussion

The adverse reactions of hypersensitivity associated with IVIG therapy affect

1% to 15% of patients (Duhem et al. 1994). Renal complications also has been attributed to IVIG, however, it remains relatively uncommon (Cantu et al. 1995; Cayco et al. 1997). Concerning renal complications of IVIG, ARF has mainly been reported in the literature (Corvetta et al. 1989; Ellie et al. 1992; Ahsan et al. 1994, 1996; Pasatiempo et al. 1994; Poullin et al. 1995; Hansen-Schmidt et al. 1996; Cayco et al. 1997). Although the cause of renal toxicity of IVIG remains a point of discussion, hyperoncotic pressure due to the stabilizer sucrose is thought to account for the cause of ARF. Typical renal biopsy findings of these cases have been reported to be proximal tubular cell swelling and vacuolization without interstitial infiltration (Ahsan et al. 1994; Cantu et al. 1995; Hansen-Schmidt et al. 1996). However, Veno I is an immunoglobulin containing no sucrose, and there is no published report to describe ARF to date (Cayco et al. 1997).

Our patient with a pre-existing renal disease of NS demonstrated chills, joint pain, dry cough and a transient decrease in the CH_{50} following IVIG treatment. Although he did not develop ARF, a renal biopsy at the time of 19 days after IVIG revealed moderate degree of tubular cell vacuolization and massive infiltration of the interstitium by mononuclear cells and eosinophils. These clinical manifestations as well as renal biopsy findings seemed to be compatible with an hypersensitivity reaction. He had been exposed to PIPC, furosemide and human albumin except for Veno I preceding the episode of acute TIN. Of these, PIPC and Veno I are most likely the cause of his TIN, since PIPC-induced hypersensitivity nephritis has been reported to date (Tanaka et al. 1997).

Renal lesion of PIPC-induced TIN has been described to be a dense lymphocytic infiltrate with marked eosinophils. These histologic character is also seen in this patient as in the patients with various drug-induced hypersensitivity nephritis (Shibsaki et al. 1991). Thus, it may be difficult to discuss the histologic character of IVIG-induced TIN in regard to the difference from that of the other drug-induced TIN.

Clinically, no adverse reaction was seen in the succeeding use of PIPC in this patient. Judging from the clinical course in which administration of Veno I led to an episode of acute TIN with recovery on its removal, thereby, IVIG is most likely the cause of his TIN.

The clinical course also indicated that the other explanations for the TIN, such as the residual urinary tract infection, were unlikely. To the best of our knowledge, there is only a published report to describe a patient with hypersensitivity nephritis probably due to IVIG treatment (Ellie et al. 1992). Renal biopy findings of their patient revealed diffuse infiltration of the interstitium by mononuclear cells and tubular atrophy with no evidence of immunoglobulin deposits. Renal lesions in our patient seems to be same as theirs, except for a weak deposition of immunoglobulin (IgM) and complements (C_3, C_4). We think that pre-existing steroid-resistant NS might, in part, account for the mesangial deposition.

Renal complications associated with IVIG treatment in patients with pre-existing renal diseases has also been reported (Hansen-Schmidt et al. 1996). However, underlying renal diseases with normal renal function is thought to be no clear risk factor for the developement of IVIG-associated renal toxicity (Cayco et al. 1997). Although the pathogenesis of TIN in our patient remains to be elucidated, a possible activation of autoimmunities, which led to a decrease in the CH_{50}, as well as underlying immunologic disorder due to minimal-change NS, might account for his TIN. However, it is difficult to draw the conclusion, since immunohistochemical studies for the interstitial infiltrate cells were not done. Further study will be needed.

Concerning renal manifestations of TIN in our patient, a transient increase in the urinary β_2-MG occurred. ARF was not observed during hospital course. Accordingly, these observation might indicate that clinically silent TIN associated with IVIG treatment exists. We therefore suggest that more attention should be paid to acute TIN when IVIG treatment is performed.

References

1) Ahsan, N., Palmer, B.F., Wheeler, D., Grrenlee, R.G., Jr. & Toto, R.D. (1994) Intravenous immunoglobulin-induced osmotic nephrosis. *Arch. Intern. Med.*, **154**, 1985-1987.
2) Ahsan, N., Wiegand, L.A., Abendroth, C.S. & Manning, E.C. (1996) Acute renal failure following immunoglobulin therapy. *Am. J. Nephrol.*, **16**, 532-536.
3) Cantu, T.G., Hoehn-Saric, E.W., Burgess, K.M., Racusen, L. & Scheel, P.G. (1995) Acute renal failure associated with immunoglobulin therapy. *Am. J. Kidney Dis.*, **25**, 228-234.
4) Cayco, A.V., Perazella, M.A. & Hayslett, J.P. (1997) Renal insufficiency after intravenous immune globulin therapy: A report of two cases and an analysis of the literature. *J. Am. Soc. Nephrol.*, **8**, 1788-1794.
5) Corvetta, A., Della Bitta, R., Gabrielli, A., Spaeth, A.G. & Danieli, G. (1989) Use of high-dose intravenous immunoglobulin in systemic lupus erythematosus: Report of three cases. *Clin. Exp. Rheumatol.*, **7**, 295-299.
6) Duhem, S., Dicato, M.A. & Ries, F. (1994) Side-effects of intravenous immune globulins. *Clin. Exp. Immunol.*, **97**, Suppl. 1, 79-83.
7) Ellie, E., Combe, C. & Ferrer, X. (1992) High-dose intravenous immune globulin and acute renal failure. *N. Engl. J. Med.*, **327**, 1032-1033.
8) Fischer, P., Naoe, S. & Gaedicke, G. (1996) Kawasaki disease: Update on diagnosis, treatment, and a still controversial etiology. *Pediatr. Hematol. Oncol.*, **13**, 487-501.
9) Hansen-Schmidt, S., Silomon, J. & Keller, F. (1996) Osmotic nephrosis due to high-dose immunoglobulin therapy containing sucrose (but not with glycine) in a patient with immunoglobulin A nephritis. *Am. J. Kidney Dis.*, **28**, 451-453.
10) Imbach, P., Barandun, S., d'Apuzzo, V., Baumgartner, C., Hirt, A., Morell, A., Rossi, E., Schoni, M., Vest, M. & Wagner, H.P. (1981) High-dose intravenous gammmaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*, **I**, 1228-1231.
11) Pasatiempo, A.M.G., Kroser, J.A., Rundnick, M. & Hoffman, B.I. (1994) Acute renal failure after intravenous immunoglobulin therapy. *J. Rheumatol.*, **21**, 347-349.
12) Poullin, P., Moulin, B., Ollier, J., Benaicha, M., Olmer, M. & Gabriel, B. (1995) Hyperoncotic acute renal failure after intravenous immunoglobulin therapy. *Presse Med.*, **24**, 441-444.

13) Shibasaki, T., Ishimoto, F., Sakai, O., Joh, K. & Aizawa, S. (1991) Clinical characterization of drug-induced allergic nephritis. *Am. J. Nephrol.*, **11**, 174–180.
14) Silverman, E.D., Laxer, R.M., Greenwald, M., Gelfand, E., Shore, A., Stein, L.D. & Roifman, C.M. (1990) Intravenous gamma globulin therapy in systemic juvenile rheumatoid arthritis. *Arthritis Rheum.*, **33**, 1015–1022.
15) Tanaka, H., Waga, S., Kakizaki, Y., Tateyama, T., Koda, M. & Yokoyama, M. (1997) Acute tubulointerstitial nephritis associated with piperacillin therapy in a boy with glomerulonephritis. *Acta Paediatr. Jpn.*, **39**, 698–700.