

STUDY INTO THE EFFECT OF AQUAPORIN-2 ON THE EFFICACY AND PREDICTED EFFECT OF TOLVAPTAN IN PATIENTS OF NEPHROTIC SYNDROME

Eiichi Sato^{1,2} Tsukasa Nakamura^{2,1} Mayuko Amaha² Mayumi Nomura² Daisuke Matsumura²
Akiko Fujii¹ Yuko Ono¹ Yoshihiko Ueda¹

Dokkyo Medical University, Koshigaya Hospital, Department of Pathology¹
Shinmatsudo Central General Hospital, Division of Nephrology, Department of Internal Medicine²

OBJECTIVES

A retrospective investigation was conducted into the efficacy and adverse drug reactions of tolvaptan in the treatment of diabetic nephropathy and MCNS (Minimal Change Nephrotic Syndrome) with heart failure, in patients for whom general diuretic monotherapy had proved ineffective.

Another aim was to investigate specific clinical parameters in responders and non-responders and to investigate the expression of aquaporin-2 in kidney tissue.

In addition, the effect of tolvaptan in patients with renal failure will be discussed and specific cases where tolvaptan would be indicated.

METHODS

The subjects of this study were 52 patients with chronic kidney disease (due to diabetic nephropathy) and MCNS with heart failure who presented to our hospital over the last 2 years and who were treated with tolvaptan.

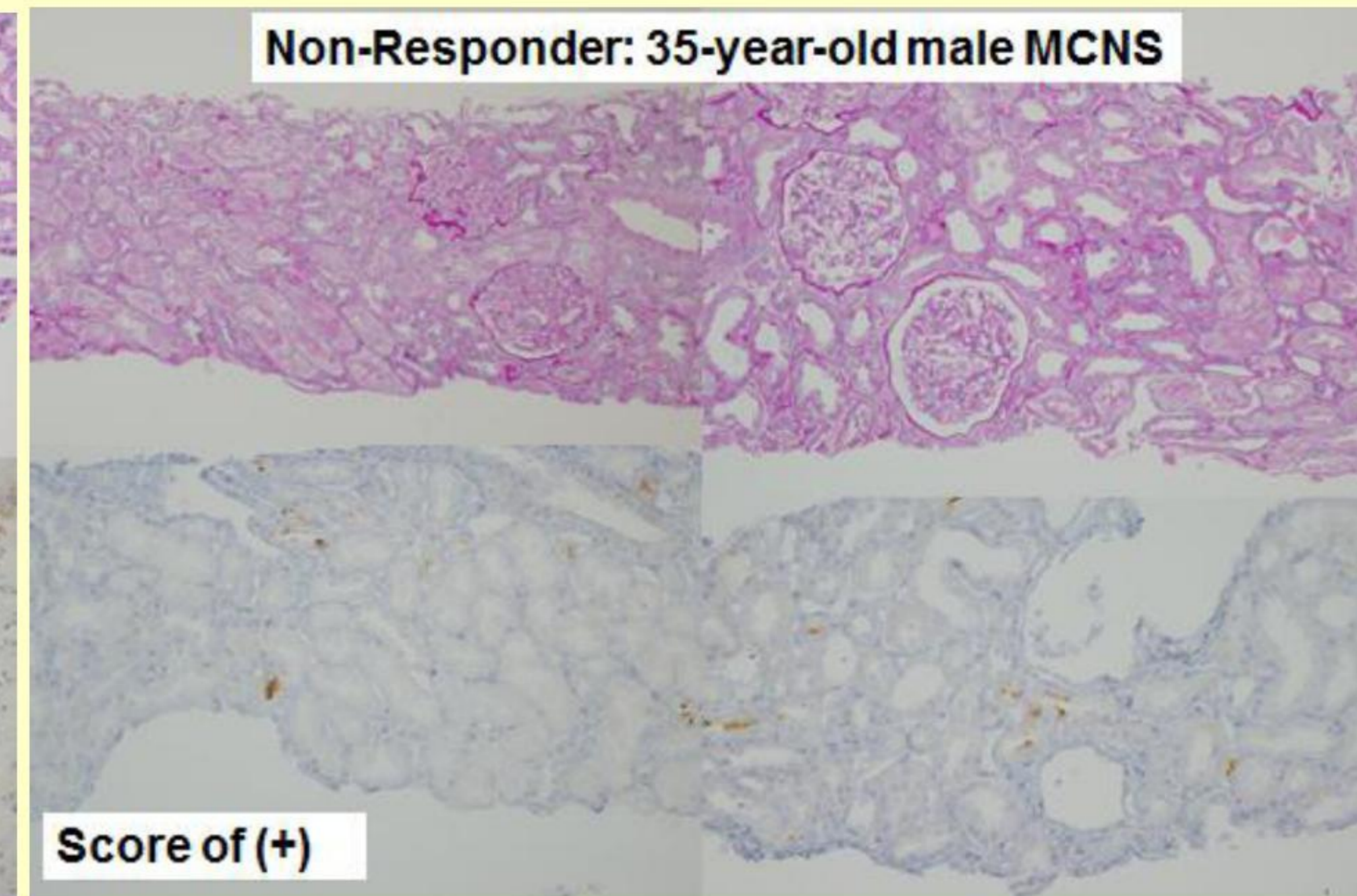
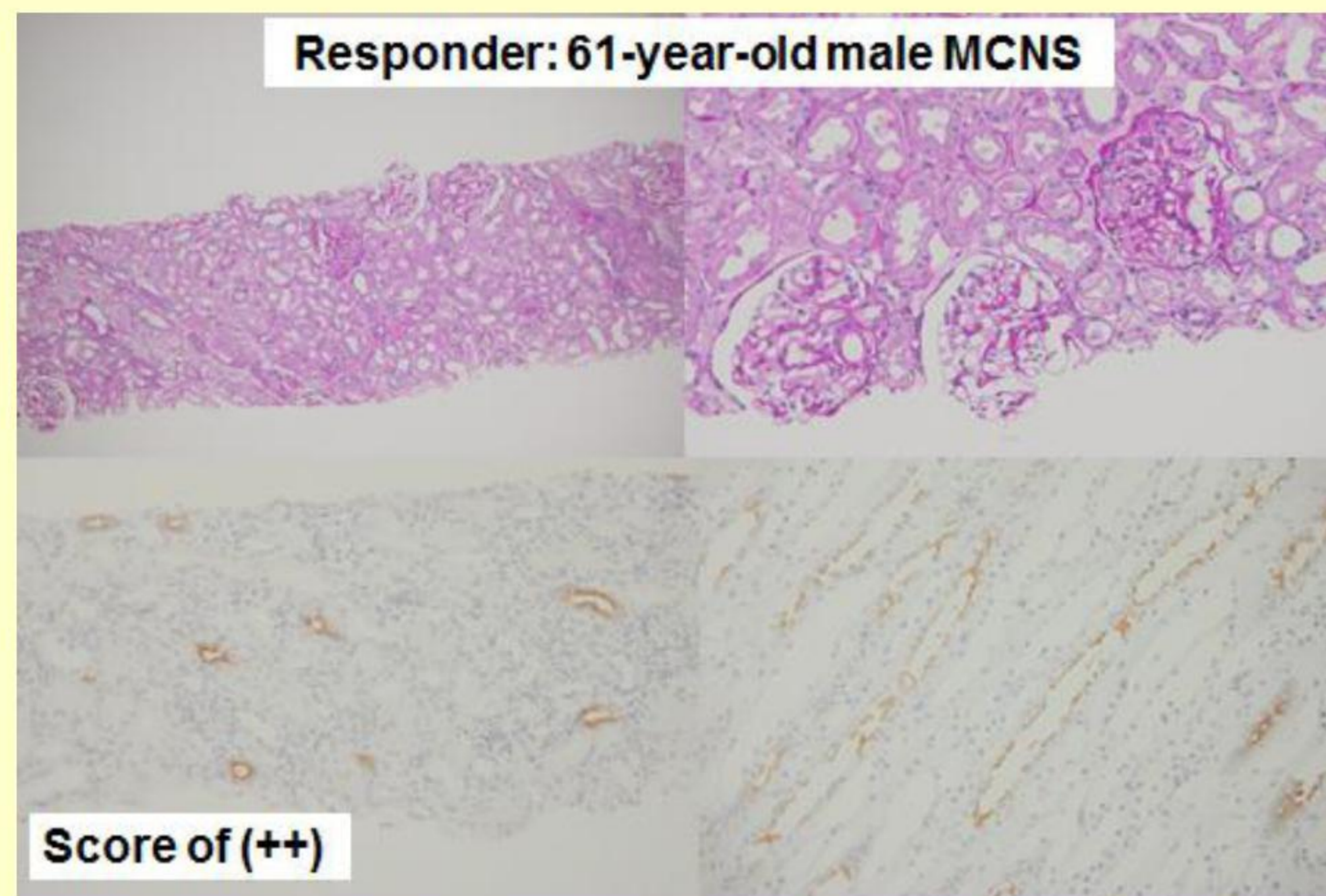
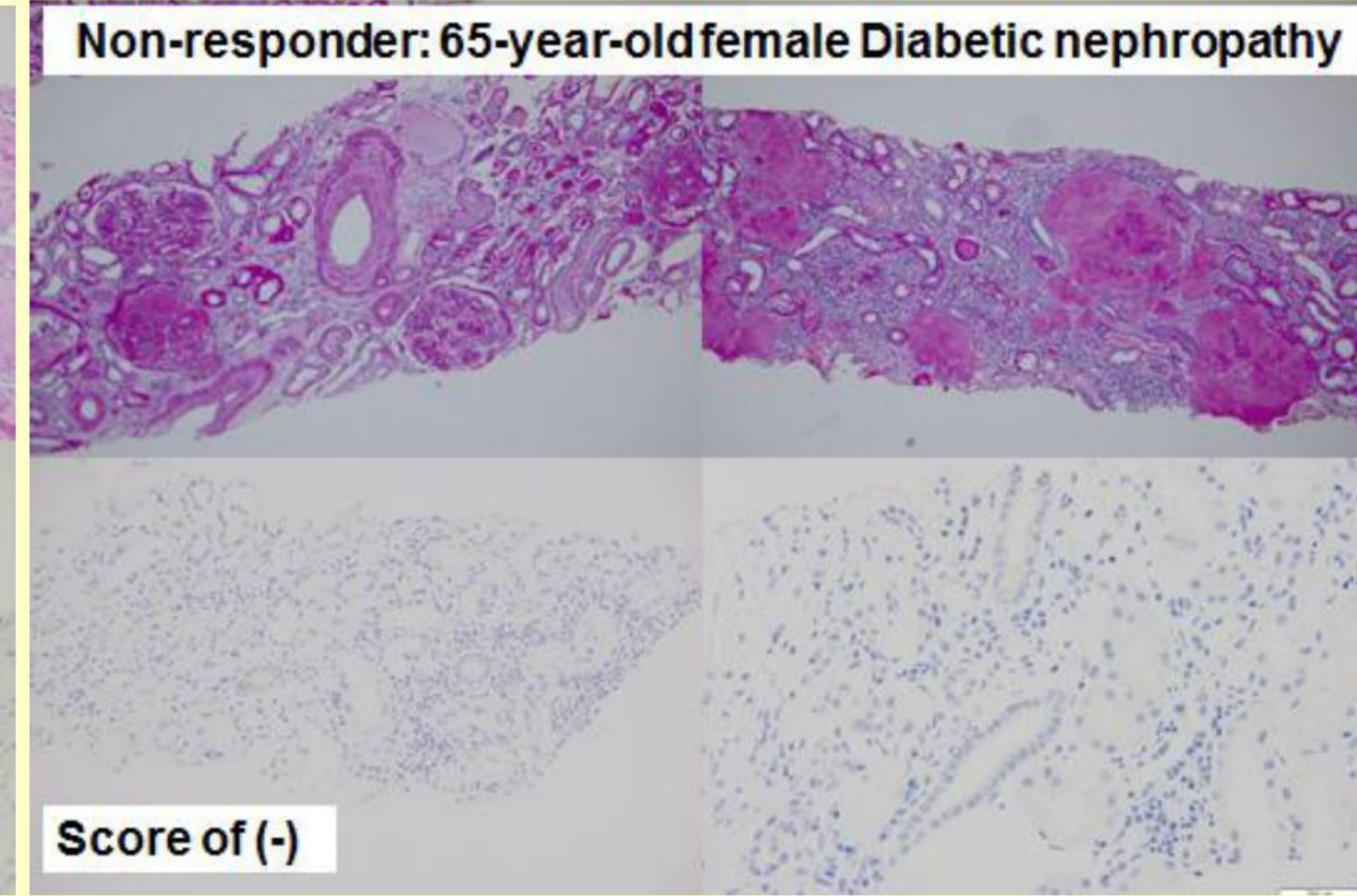
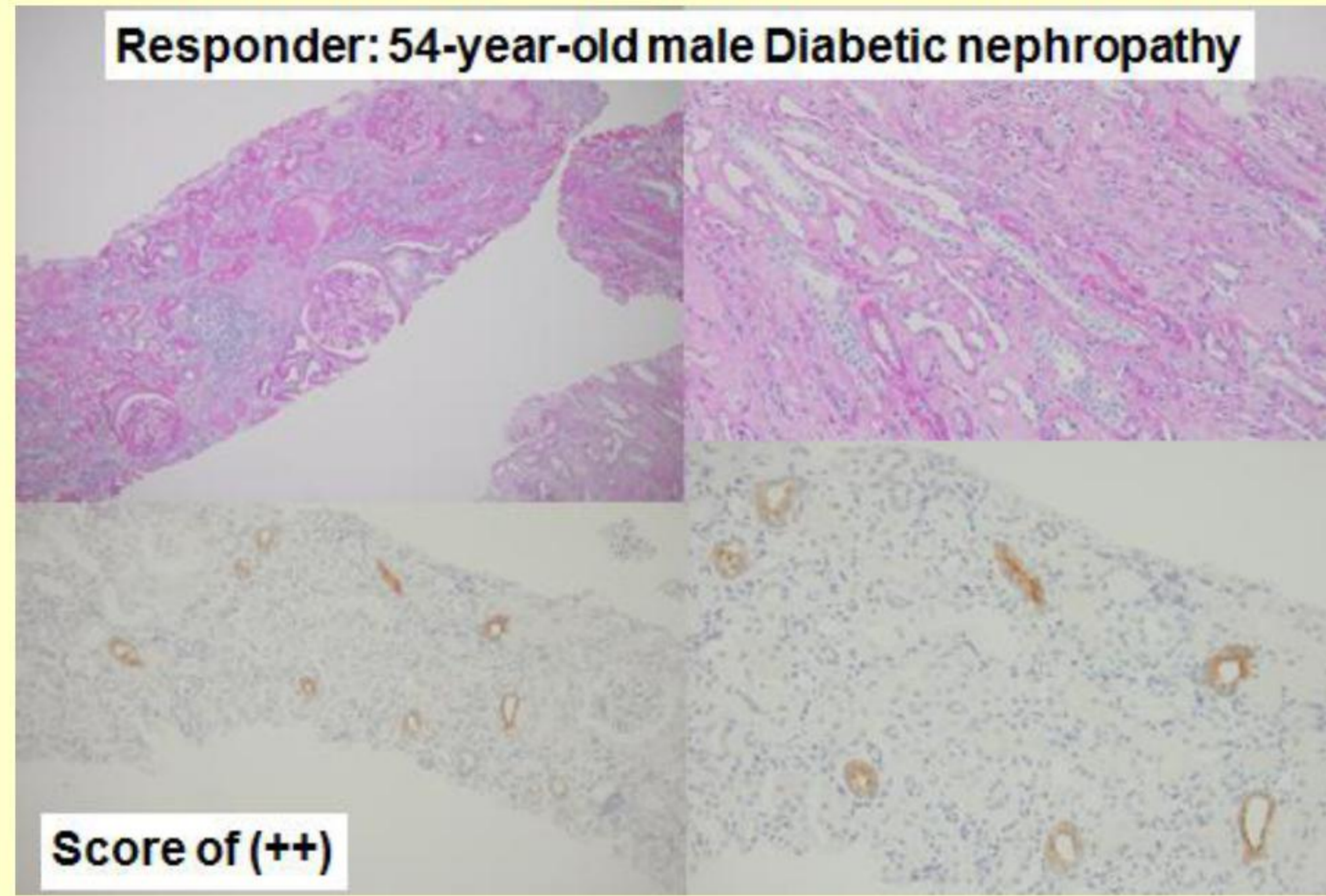
Tolvaptan was administered as a single oral dose of 7.5-15 mg per day depending on systemic state and water intake and on a case-by-case basis. The endpoints investigated were urinary output after drug administration, physical findings, and blood analyses before and/or after administration of tolvaptan.

We defined effective cases as those showing a 2-fold increase in urinary volume compared to pre-administration levels or a clear improvement in edema or heart failure symptoms.

Immunohistochemistry was also used to examine aquaporin-2 expression in the epithelial cells of the collecting duct (the site of tolvaptan action) and its relationship to the efficacy of tolvaptan. Results were evaluated using 4 scores. A score of (-) is assigned when the collecting duct shows no staining; a score of (+) is assigned when less than 25% is stained; a score of (++) is assigned when at least 50% of the biopsy specimens is stained.

RESULTS

| | Responders (26) | Non-Responders (14) | p-value |
|-------------------------------------|-----------------|---------------------|---------|
| Age | 62.5±13.0 | 67.4±11.4 | 0.77 |
| Gender (Male) | 16 | 11 | 0.61 |
| Pre Urine Volume (mL) | 652.9±477.9 | 1090±385.1 | 0.15 |
| Post Urine Volume (mL) | 2499.5±1314.9 | 900±500 | 0.42 |
| Pre Cre mg/dL | 3.4±2.5 | 6.3±3.0 | <0.01 |
| Post Cre mg/dL | 3.5±2.5 | 6.1±2.7 | 0.68 |
| Pre eGFR ml/min/1.73m ² | 25.7±19.7 | 10.1±6.8 | <0.01 |
| Post eGFR ml/min/1.73m ² | 24.9±19.5 | 9.9±8.5 | 0.01 |
| Pre Alb g/dL | 2.9±0.5 | 2.9±0.6 | 0.66 |
| Pre Na mEq/L | 129.0±3.4 | 138.9±4.3 | 0.95 |
| Post Na mEq/L | 141.9±2.9 | 139.0±5.2 | 0.11 |
| Pre BNP pg/mL | 483.7±389.7 | 1485.1±1935.4 | 0.03 |
| Post BNP pg/mL | 204.6±128.6 | 590.3±331.7 | (HD) |



| | Responders (9) | p-value |
|-------------------------------------|----------------|---------|
| Age | 57.3±17.7 | |
| Gender (Male) | 9 | |
| Pre Urine Volume (mL) | 567.8±338.9 | 0.007 |
| Post Urine Volume (mL) | 1832.2±619.4 | |
| Pre Cre mg/dL | 1.6±0.4 | 0.76 |
| Post Cre mg/dL | 1.8±1.0 | |
| Pre eGFR ml/min/1.73m ² | 42.3±19.4 | 0.68 |
| Post eGFR ml/min/1.73m ² | 43.4±27.0 | |
| Pre Alb g/dL | 2.1±0.3 | |
| Pre Na mEq/L | 136.1±3.7 | 0.07 |
| Post Na mEq/L | 139.0±4.5 | |

| | Non-Responders (3) |
|----------------|--------------------|
| Age | 34.6±5.5 |
| Gender (Male) | 2 |
| Pre Cre mg/dL | 1.0±0.1 |
| Post Cre mg/dL | 3.0±1.0 |
| Pre Alb g/dL | 1.7±0.2 |

CONCLUSIONS

1. Of the 56 cases, 49 were tolvaptan responders. No problematic side effects were observed.
2. Comparison of tolvaptan responders and non-responders indicated that serum Cre levels were significantly lower in responders. Serum BNP levels decreased significantly after administration in responders.
3. Diabetic nephropathy and nephrotic syndrome responders exhibited aquaporin 2 expression in collecting duct epithelial cells. No expression or weak positive expression was observed in diabetic nephropathy and in MCNS non-responders.

REFERENCES:

Sato E, et al. Effect of tolvaptan in patients with chronic kidney disease due to diabetic nephropathy with heart failure. Int Heart J. 2014;55:533-8.

