A Patient With Minimal Change Disease and Acute Focal Tubulointerstitial Nephritis Due To Traditional Medicine: A Case Report and Small Literature Review

Keun-Hyeun Lee, KMD,[1,2] Han-Sol Jeong, PhD, KMD,[3,#] and Harin Rhee, MD[4,5]

Gongjin-dan (GJD) is a traditional formula that is widely used in Korea and China, and it has been used from 1345 AD in China to improve the circulation between the kidneys and the heart and to prevent all diseases. However, its adverse effects have not yet been reported. We present a patient with minimal change disease and focal tubulointerstitial nephritis associated with GJD. A 72-year-old man visited the clinic for generalized edema 20 days after starting GJD. His serum albumin level was low and nephrotic-range proteinuria was detected. A kidney biopsy showed minimal change disease and acute tubulointerstitial nephritis. After stopping GJD, a spontaneous complete remission was achieved. We discuss the possible pathogenesis of GJD-induced minimal change disease and review the adverse effects of GJD's ingredients and traditional Chinese medicines that can induce proteinuria. We report a new adverse effect of GJD, which might induce increased IL-13 production and an allergic response, leading to minimal change disease and focal tubulointerstitial nephritis.

Key words: Acute interstitial nephritis, minimal change nephrotic syndrome, adverse effect, toxin, TCM, nephrotoxin

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INTRODUCTION

Gongjin-dan (or Gongchen-dan, GJD) is a traditional multi-formula composed of two animal and two herbal products: musk (*Moschus moschiferus* Linne), red deer antler (*Cervus elaphus* sibiricus), Korean angelica root (*Angelica gigas* Nakai), and Japanese cornelian cherry (*Cornus officinalis* Sieb. Et Zucc.). GJD was first described in the traditional Chinese medical literature and was called Shi Yi De Xiao Fang by Yi-lin Wei in 1345 AD. In this literature, GJD was considered to be a great medicine that improved the circulation between the *Shen* (*kidneys/water*) and the *Xin* (*heart/fire*) in traditional Chinese medicines (TCM) terminology and prevented all diseases; thus, this formula was used by the Emperor. GJD is still widely used in Korea and China as an anti-fatigue, anti-aging, and tonic agent to enhance memory and learning.[1] GJD is also used for patients with stroke due to its neuro-protective effect.[2] Traditionally, GJD has been known to be a safe medicine, and the adverse effects of GJD have not been well studied. However, we observed a case of nephrotic syndrome in the setting of GJD use. We report a patient with minimal change disease (MCD) and acute focal tubulointerstitial nephritis (ATIN) associated with GJD and perform a literature review on the adverse effects of each GJD ingredient and TCM that can cause proteinuria.

CASE PRESENTATION

In December 2012, a 72-year-old Korean man with a 10-year history of hypertension visited our clinic complaining of generalized edema. Three weeks prior to admission, he had eaten GJD once a day for 20 days. On admission, a physical examination demonstrated a body temperature of 36.5°C, a blood pressure of 110/60 mmHg, a heart rate of 68 beats/min, and a respiratory rate of 20 breaths/min. His body weight was 64.45 kg, which represented a 2-kg increase in two weeks, and he had marked, pitting pre-tibial edema. In the initial blood tests, WBC count was 7790/μL with mild eosinophilia (differential count 7.5% and absolute eosinophil count 584/μL). The initial hemoglobin level was 11.7 g/dL. The total protein and serum albumin levels were slightly

1 Graduate School of Korean Medicine, Pusan National University, Yangsan, Gyeongsangnam-do, Republic of Korea
2 Hemin Traditional Korean Medical Clinic, Busan, Republic of Korea
3 Division of Applied Medicine, School of Korean Medicine, Pusan National University, Yangsan, Gyeongsangnam-do, Republic of Korea
4 Department of Internal Medicine, Pusan National University School of Medicine, Busan, Republic of Korea
5 Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea

Correspondence address: Han-Sol Jeong, PhD, KMD, Division of Applied Medicine, School of Korean Medicine, Pusan National University, Beomeo-ri, Mulgeum-eup, Yangsan-si, Gyeongsangnam-do, Republic of Korea 626-870
e-mail: jhsol33@pusan.ac.kr

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decreased (total protein: 5.9 g/dL and albumin: 3.2 g/dL), but his renal function was preserved [blood urea nitrogen (BUN) 16.5 mg/dL and serum creatinine 0.95 mg/dL]. His serum glucose level was normal (fasting serum glucose: 96 mg/dL). However, his urine test showed markedly abnormal findings. His urine was maximally diluted (urine-specific gradient < 1.005), and nephrotic-range proteinuria was found [spot urine protein/creatinine ratio (PCR), 6810.23 mg/g]. Hematuria and pyuria were not present. All of the other serologic parameters, including complement factors C3 and C4, antinuclear antibody, anti-glomerular basement membrane antibody, and anti-neutrophil cytoplasmic antibodies, were negative. His chest X-ray showed mild pulmonary congestion.

The next day, a percutaneous left kidney biopsy was performed under ultrasound guidance. Light microscopy showed normal glomerular size and architecture (Figure 1A). The tubulointerstitium showed mild patchy atrophy and fibrosis consistent with aging, and focal leukocyte infiltration was found in the tubules and interstitium (Figure 1B). Immunofluorescence was negative for immunoglobulin G, A, and M. Electron microscopy showed characteristic diffuse foot process effacement, and electron-dense deposits were not identified (Figure 1C). Based on these biopsy findings, he was diagnosed with MCD and focal ATIN associated with GJD.

To determine the patient's GJD dose and duration of use, we interviewed the doctor who had prescribed GJD. His GJD was composed of 1.28 g each of red deer antler, Japanese cornelian cherry, and Korean angelica root and 0.16 g of musk. Musk that had permission from Ministry of Korean Food and Drug Safety was used. He prescribed four grams of GJD per day for 20 days. During that period, there was no concurrent medication except antihypertensive drug. We also found that the GJD was stopped after the patient developed generalized edema.

On admission, symptomatic treatment with diuretics was started. Although nephrotic-range proteinuria was observed on presentation, his serum albumin level was only slightly decreased; thus, we delayed steroid therapy while waiting for the urine PCR test. After two weeks of supportive therapy, his edema was controlled, his serum albumin level increased to 3.7 mg/dL, and his urine PCR decreased to the normal range (135 mg/g). Eight months after his initial presentation, the patient was feeling well with no recurrence of edema.

DISCUSSION

We have presented a patient with MCD and focal ATIN associated with GJD.

MCD is one of the most common causes of nephrotic syndrome, accounting for 10–15% cases of nephrotic syndrome in adults.[3,4] Although, the cause of MCD is mostly idiopathic, MCD can also be caused by certain drugs, such as a non-steroidal anti-inflammatory drug (NSAID) and interferon.[5,6] ATIN is an uncommon hypersensitivity reaction to a drug that is not dose related and can occur anywhere between 5 and 35 days after initiating a medication. ATIN is usually accompanied by acute kidney injury, systemic eosinophilia, fever, and rash; however, there are some patients who do not have all of these features.[7–9] The diagnosis of ATIN is confirmed by the kidney biopsy.

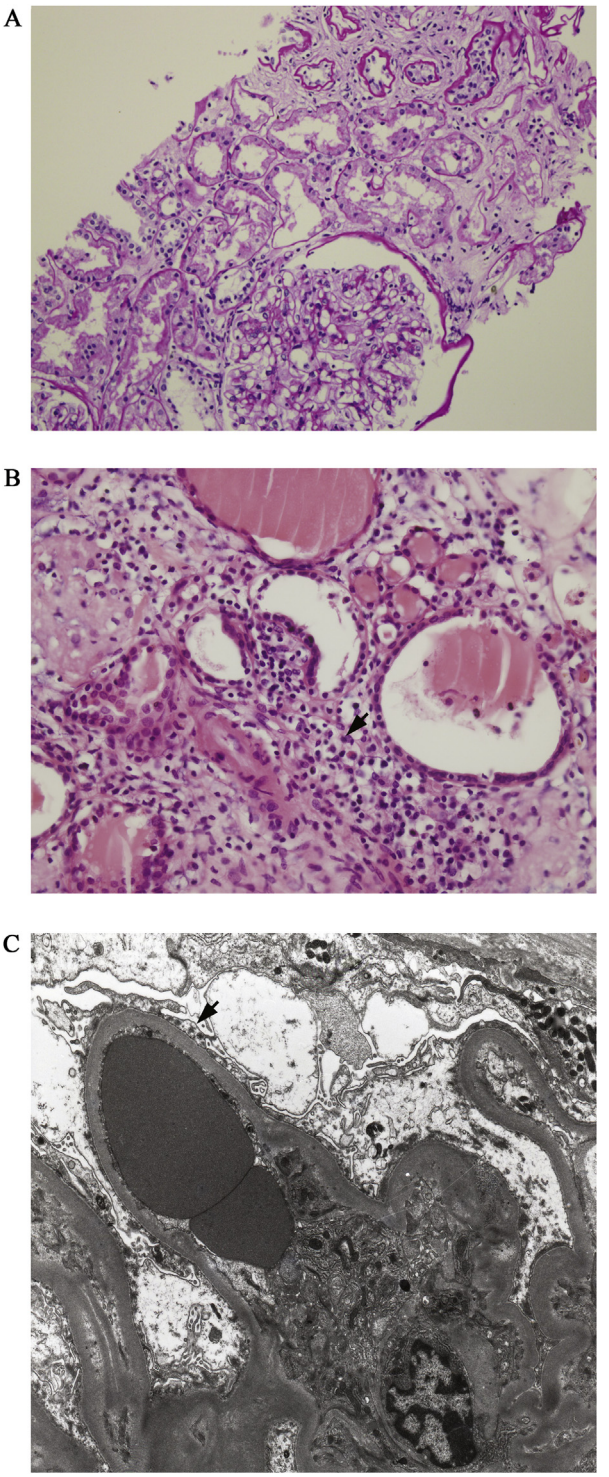

Figure 1. Kidney biopsy findings for the patient. (A) Light microscopy showed normal glomerular size and architecture. The tubulointerstitium showed mild atrophy and fibrosis consistent with aging. (B) Light microscopy showed focal tubulointerstitial nephritis; the neutrophils accumulated in the tubules and interstitium (arrow). (C) Electron microscopy showed diffuse foot process effacement (arrow), which is a characteristic feature of MCD. (A) Periodic acid-Schiff, ×200; (B) hematoxylin and eosin, ×400; and (C) ×3000.