# Membranous Nephropathy Associated With Fluconazole Treatment

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About 6% to 9% of cases of membranous nephropathy develop secondary to exposure to drugs. Fluconazole is a widely used antifungal agent that was never implicated in the development of membranous nephropathy. We report the case of a patient found to have membranous nephropathy secondary to fluconazole treatment. This patient had recurrent episodes of nephrotic syndrome caused by readministration of fluconazole. This is the first reported case of membranous nephropathy caused by fluconazole treatment and the first case report of the clinical course of recurrent membranous nephropathy caused by reexposure to this medication.
*Am J Kidney Dis* 49:318-322. 

***INDEX WORDS:*** Membranous nephropathy; fluconazole; proteinuria.

Membranous nephropathy is the most common cause of nephrotic syndrome in adults. It usually is idiopathic, and 21% to 25% of cases occur secondary to such identifiable causes as systemic lupus nephritis, malignancies, hepatitis B, and use of drugs.[1] Drugs appear to be the cause of membranous nephropathy in 6% to 9% of cases, and a variety of drugs were reported in association with its development.[1] Gold and penicillamine used in patients with rheumatoid arthritis are typical examples of causative drugs.[2,3] Nonsteroidal anti-inflammatory drugs also were implicated in the development of membranous nephropathy.[4,5] Anti–tumor necrosis factor $\alpha$ agents used in patients with rheumatological diseases and 2-mercaptopropionylglycine to treat cystinuria also were associated with membranous nephropathy.[6,7] Fluconazole is a widely used synthetic triazole antifungal agent. It generally is well tolerated and never was reported as a cause of nephropathies. We report the case of a patient administered a once-weekly dose of fluconazole[8,9] for resistant tinea pedis who subsequently developed membranous nephropathy.

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*Received September 13, 2006; accepted in revised form November 9, 2006.*

*Originally published online as doi:10.1053/j.ajkd.2006.11.033 on January 3, 2007.*

*Support: None. Potential conflicts of interest: None.*

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*0272-6386/07/4902-0018$32.00/0*

*doi:10.1053/j.ajkd.2006.11.033*

## CASE REPORT

A 58-year-old woman presented with increasing generalized edema accompanied by nausea and indigestion for 3 weeks in February 2005. The patient had a history of hypertension for 10 years and cervical cancer (carcinoma in situ), for which she underwent total abdominal hysterectomy in 1998, and had been followed up with yearly Papanicolaou smears thereafter. She had been administered amlodipine for hypertension, and recently, hydrochlorothiazide, metoclopramide, and levosulpiride (Levopride; SK Pharmaceuticals, Korea) were prescribed by a primary care physician. No other medication history was obtained at initial presentation. Physical examination showed blood pressure of 146/97 mm Hg, clear breath sounds, and $3^+$ lower-extremity pitting edema. Serum creatinine level was 2.6 mg/dL (230 $\mu$mol/L). Serum albumin level was 1.7 g/dL (17 g/L). Urinary protein excretion was 21 g/d by means of urinary protein-creatinine ratio. Serological test results for antinuclear antibody, antineutrophil cytoplasmic antibody, hepatitis B surface antigen, and hepatitis C antibody were negative. Immunologic test results for antistreptolysin O titer, C3, C4, and C-reactive protein were within normal range. Urine microscopy showed 8 red blood cells and 10 white blood cells per high-power field. Abdomen and kidney ultrasound study findings were unremarkable.

One week after initial presentation, a percutaneous renal biopsy was performed. Light microscopy showed 15 glomeruli, 1 of which was globally sclerotic. Glomerular tufts showed normal cellularity, and the glomerular capillary wall did not seem to be thickened. Immunofluorescence studies showed granular staining mainly for immunoglobulin G and C3 along the glomerular basement membrane (GBM). Electron microscopy showed subepithelial immune deposits along the GBM and epithelial foot-process effacement. Immune deposits were widely dispersed and separated by uninvolved GBM. These findings indicate that the patient had stage I membranous nephropathy (Fig 1).

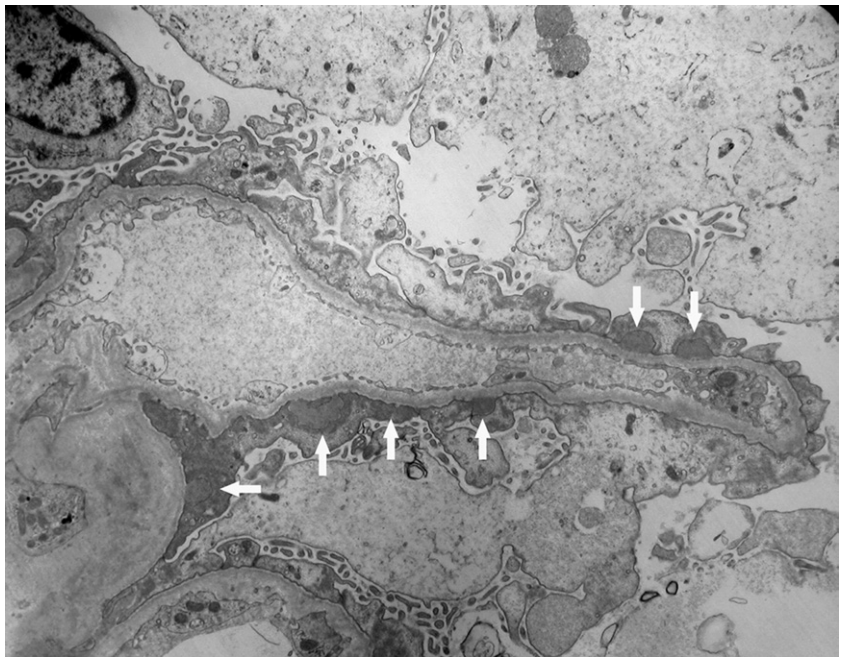

**Figure 1.** Renal biopsy findings. Electron microscopy shows subepithelial dense deposits and foot-process effacement. Arrows represent subepithelial immune deposits. Note that immune deposits are widely dispersed and separated by uninvolved GBM.

After the diagnosis, the patient was sent back to the cancer center, where cervical cancer surgery was performed to evaluate for recurrence. There was no evidence of recurrence. Esophagogastroduodenoscopy, colonoscopy, and mammogram were all negative for malignancy. Two months after initial presentation, she returned to our renal clinic and underwent follow-up blood and urine tests. Surprisingly, urine test results were negative for protein, and serum albumin level was 4.0 g/dL (40 g/L). At this clinic visit, amlodipine was changed to valsartan therapy. Follow-up tests in 1 month confirmed recovery from nephrotic syndrome. Approximately 5 months after initial presentation, the patient returned to the clinic with reports of increasing pedal edema. Laboratory tests showed relapse of nephrotic syndrome. Because her clinical course was difficult to understand, she was asked to return to the clinic in 2 weeks for repeated laboratory tests.

Surprisingly, repeated tests showed resolution of proteinuria, again with increasing serum albumin levels. The patient was questioned about whether she was using drugs other than those prescribed by our clinic, and she reported that she had been using once-weekly doses of fluconazole for tinea pedis, prescribed by a doctor in her hometown. The drug store in her hometown was contacted, and prescription records were obtained; she had been using fluconazole, 150 mg/wk, continuously for 1 year until 3 weeks before the initial presentation, and then intermittently after that, only when she returned to her hometown. The temporal relationship between nephropathy onset and fluconazole intake seemed apparent; hence, she was instructed not to use the fluconazole. In addition, valsartan therapy was discontinued without prescribing other antihypertensive drugs to remove any confounding factors.

Laboratory tests in 3 weeks confirmed recovery from proteinuria. About 6½ months after the initial presentation, the patient returned to the clinic with relapsing pedal edema, and her laboratory tests showed relapse of nephrotic syndrome. The patient reported that she could not resist resuming fluconazole therapy because of her annoying tinea pedis, and this was confirmed by recontacting the drug store. The instruction was emphasized, and she was sent home with amlodipine and torasemide therapy. Off fluconazole therapy, the patient went into complete remission again in approximately 2 months. Since this episode, she has not resumed fluconazole therapy and has had no relapse observed during the past 10 months. Her clinical course is shown in Fig 2.

## DISCUSSION

Fluconazole is a widely used antifungal agent that has never been described as a cause of nephropathies. In this report, for the first time, we describe a case implicating fluconazole in the development of membranous nephropathy. Additionally, this report describes clinical events of membranous nephropathy when the causative drug is readministered after resolution of the disease.

When nephrotic syndrome recurred in our patient, she was instructed to stop using fluconazole; however, she resumed fluconazole therapy on returning to her hometown and subsequently developed nephrotic syndrome again. Although unfortunate for the patient, this episode mimicking a prospective rechallenge experiment made the relationship between fluconazole and membranous nephropathy more evident. The observa-