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Successful Treatment of *Paecilomyces variotii* Pneumonia and Lupus Nephritis With Posaconazole-Cyclophosphamide Co-administration Without Drug Interaction–Induced Toxicity

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Paecilomyces variotii is an opportunistic mold that causes pulmonary infections in immunosuppressed humans that are often treated with triazole therapy. Lupus nephritis is a major cause of progressive kidney disease in patients with systemic lupus erythematosus, often requiring cyclophosphamide-based therapies. Triazole-cyclophosphamide co-administration is challenging as triazoles increase cyclophosphamide concentrations, which can worsen cyclophosphamide toxicity. We describe herein a patient with *Paecilomyces variotii* pneumonia and concomitant lupus nephritis who was successfully treated with posaconazole and echinocandin-bridged interruptions to allow for cyclophosphamide therapy. This regimen was well-tolerated without cyclophosphamide toxicity and achieved improvements in both fungal pneumonia and renal function.

Keywords. cyclophosphamide; drug–drug interactions; lupus nephritis; *Paecilomyces*; posaconazole.

Paecilomyces variotii is a saprophytic hyalohyphomycete that causes infection in susceptible humans [1, 2]. It is found ubiquitously in soil and organic materials including decaying plants, wood, and foodstuffs [3]. *Paecilomyces* is a genus including certain species that have been reclassified into the genus *Purpureocillium*, including *Purpureocillium lilacinum* (formerly *Paecilomyces lilacinus*), which can be differentiated from *P variotii* using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) Biotyper database or sequencing methods [4]. Though human infection is rare, a range of disease has been described including pneumonia [5], endocarditis [6], keratitis [7], peritonitis [8], fungemia [9], mycetoma [3], and disseminated infections [10]. Though typically *Paecilomyces* infections have been described in immunocompromised individuals, there have been case reports of infection in patients without a known immunodeficiency [11], often after trauma or a procedure thought to serve as a method of fungal inoculation [10]. Newer-generation triazoles, particularly posaconazole, are a mainstay of therapy for patients with *Paecilomyces* infection [2], who require long courses of therapy, thereby being at risk for cytochrome P450 (CYP) system-associated drug–drug interactions [12].

We describe a patient with *P variotii* pneumonia and concomitant lupus nephritis successfully treated with posaconazole and cyclophosphamide. Lupus nephritis is the most common cause of kidney injury in patients with systemic lupus erythematosus (SLE) and carries a high risk of progressive kidney disease [13, 14], often requiring cyclophosphamide-based treatment to prevent ongoing deterioration of renal function [15, 16]. Cyclophosphamide and triazoles share a common metabolic pathway via CYP3A4 and CYP2C9 [12, 17], resulting in a clinical challenge with co-administration [17]. A randomized study comparing antifungal prophylaxis with itraconazole versus fluconazole attributed increasing hyperbilirubinemia and elevations in serum creatinine in the itraconazole group to co-administration with cyclophosphamide. The protocol was amended on interim analysis to separate dosing of itraconazole from cyclophosphamide and later was terminated early in part due to the different safety profiles of the 2 regimens [18]. Importantly, this study found a trend in doubling of creatinine

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Table 1. Laboratory Evaluation of Our Patient at Baseline and During the Course of Cyclophosphamide-Posaconazole Co-administration

			Cycle 1					Cycle 2							
Laboratory Value	Normal Range	Pre-cyclophosphamide Day −24 From Cycle 1	Day −2	Day −1	Day 0	Day +1	Day +3	Day −3	Day +1	Day +2	Cycle 3 Day +1	Cycle 4 Day +1	Cycle 5 Day +1	Cycle 6 Day +1	Cycle 7 Day +1
SCr, mg/dL	0.55–1.02	0.9	1.36	1.28	1.07	0.97	0.83	1.46	1.04	1.17	1.44	1.32	1.17	0.95	0.76
WBC, K/μL	3.98–10.04	4.76	14.49	13.09	21.14	18.32	10.55	18.2	21.15	12.99	13.05	6.15	10.39	9.31	9.32
AST, U/L	5–34	12	17	38	30	18	10	17	47	43	17	66	18	61	20
ALT, U/L	0–55	6	19	21	28	30	19	17	36	37	14	92	13	54	20
Tbil, mg/dL	0.2–1.2	0.2	0.4	0.2	0.2	0.2	0.5	0.4	0.3	0.4	0.3	0.3	0.3	0.2	0.3
ESR, mm/h	0.0–42.0	81	33	25	…	14	12	7	…	…	31	…	16	…	30
CRP, mg/L	0.0–5.0	8	7.8	4.4	1.5	0.5	0.3	0.1	…	…	0.2	13	0.8	…	1.5
11-Deoxycortisol, ng/dL	10.0–79.0	498	…	…	…	…	…	…	…	…	…	…	…	…	…
11-Deoxycorticosterone, ng/dL	<10.0	25	…	…	…	…	…	…	…	…	…	…	…	…	…
ACTH, pg/mL	5.0–46.0	115	…	…	…	…	…	…	…	…	…	5.2	…	…	…
Aldosterone, ng/dL	≤26	<3.0	…	…	…	…	…	…	…	…	…	…	…	…	…
Renin, ng/mL/h	2.9–10.8	<0.6	…	…	…	…	…	…	…	…	…	12	…	…	…
CMV, log IU/mL	Negative	…	…	…	…	…	…	…	…	…	…	6.02	Negative	Negative	…
Total complement, U/mL	30–75	55	…	…	…	…	…	…	…	…	…	…	…	…	…
C3 complement, mg/dL	83–193	70	…	…	61	…	…	…	61	…	101	…	90	101	124
C4 complement, mg/dL	15–57	16	…	…	17	…	…	…	17	…	24	…	15	21	24
Anti-dsDNA antibody, IU/mL	<30	133	…	…	51.5	…	…	…	16.9	…	22.1	19.9	18.7	15.4	16.8
UCr, mg/dL	45–106	74	…	43	88	…	35	…	…	…	28	179	192	144	88
UPr, mg/dL	1.0–14.0	386	…	115	259	…	197	…	…	…	24	125	198	98	72
UPr/UCr ratio, mg/g	<200	5216	…	2674	2943	…	5629	…	…	…	857	698	1031	681	818
Posaconazole level, ng/mL	…	…	1810	723	360	115	…	4010	171	905	216	<50	284	296	168

Abbreviations: ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CRP, C-reactive protein; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; SCr, serum creatinine; Tbil, total serum bilirubin; UCr, urine creatinine; UPr, urine total protein; WBC, white blood cells.

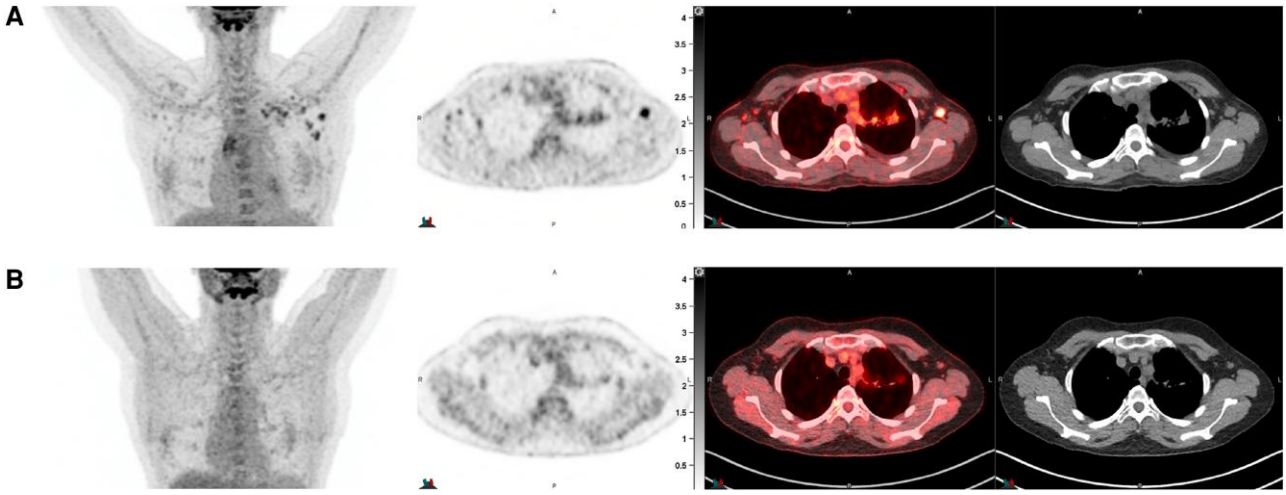

Figure 1. Improvement of *Paecilomyces variottii* pneumonia with posaconazole treatment. Shown are representative positron emission tomography (PET)/computed tomography (CT) images of the patient's chest with fluorodeoxyglucose avidity mapped. *A*, Coronal maximum intensity projection image, axial PET, PET/CT overlay, and axial CT scan from left to right, about 1 week after switching therapy from itraconazole to posaconazole. *B*, The same sequence of images 6 months later at the time of the sixth cycle of cyclophosphamide.

in patients on itraconazole versus fluconazole on interim analysis that was not seen in patients after the amendment as well as significantly more patients with tripling of their baseline total bilirubin. Further study showed that cyclophosphamide metabolites known to be hepatotoxic were present in serum at higher concentrations in the itraconazole group [17]. Physiologically based pharmacokinetic models showed that itraconazole increased the geometric mean area under the curve (AUC) of a single dose of cyclophosphamide by 17% compared to 10% with fluconazole and 76% with ketoconazole. Moreover, the AUC of cyclophosphamide after multiple doses was increased by 63% with itraconazole, 29% with fluconazole, and 102% with ketoconazole, with differences attributed to differing degrees of triazole-mediated impact on the P450 system [19].

We describe here the successful administration of 7 cycles of cyclophosphamide with posaconazole, which was temporarily paused to allow for cyclophosphamide administration. To our knowledge, we describe the first case of successful treatment of *Paecilomyces* pneumonia and lupus nephritis with posaconazole and cyclophosphamide without drug interaction–induced nephrotoxicity, hepatotoxicity, or myelotoxicity.

CASE REPORT

A 43-year-old woman immigrated to the United States from Brazil in 2019 with a history of hypothyroidism, untreated latent tuberculosis infection (LTBI), and SLE manifesting with arthralgias and fevers treated intermittently with hydroxychloroquine and prednisone. She presented with 3 months of intermittent cough, dyspnea, myalgias, and subjective fevers. These symptoms were attributed to an SLE flare, prompting initiation of prednisone (60 mg/day; 1 mg/kg/day). When symptoms persisted, she had a chest radiograph that showed a left upper lobe infiltrate that was treated empirically with levofloxacin and prednisone cessation. Four months into her symptoms, she underwent bronchoscopy with culture of bronchoalveolar lavage fluid positive for *P variotii* (minimum inhibitory concentrations [MICs] to tested antifungals: amphotericin B ≤0.03 μg/mL, isavuconazole 16 μg/mL, itraconazole ≤0.03 μg/mL, voriconazole 4 μg/mL, posaconazole ≤0.03 μg/mL, olorofim 0.25 μg/mL; minimum effective concentration [MEC] to micafungin: ≤0.015 μg/mL) [20] identified on MALDI-TOF. Susceptibility testing for antifungals including olorofim was performed at the Fungus Testing Laboratory, San Antonio, Texas. Itraconazole was initiated (200 mg every 12 hours) and hydroxychloroquine was held. A computed tomography (CT) scan of the chest 2 weeks later showed persistent consolidation and a mass-like opacity in the left upper lobe. She was then referred to the National Institutes of Health.

Laboratory analysis revealed a normal white blood cell count (4760 cells/μL), hypokalemia (3.2 mmol/L), and C-reactive protein of 8.0 mg/L. Serum creatinine was 0.99 mg/dL with an estimated glomerular filtration rate (eGFR) of 70 mL/minute/1.73 m^2 (detailed laboratory values are shown in Table 1). Itraconazole was stopped and posaconazole (300 mg/day) was initiated. She had developed new-onset hypertension over the previous month (maximal blood pressure, 179/111 mm Hg). A chest CT showed left upper lobe consolidation and a 1.8- cm nodule, which was fluorodeoxyglucose (FDG) avid on positron emission tomography (PET)/CT scan with accompanying PET-avid left axillary and subpectoral lymphadenopathy (Figure 1*A*). A sinus CT was unremarkable.

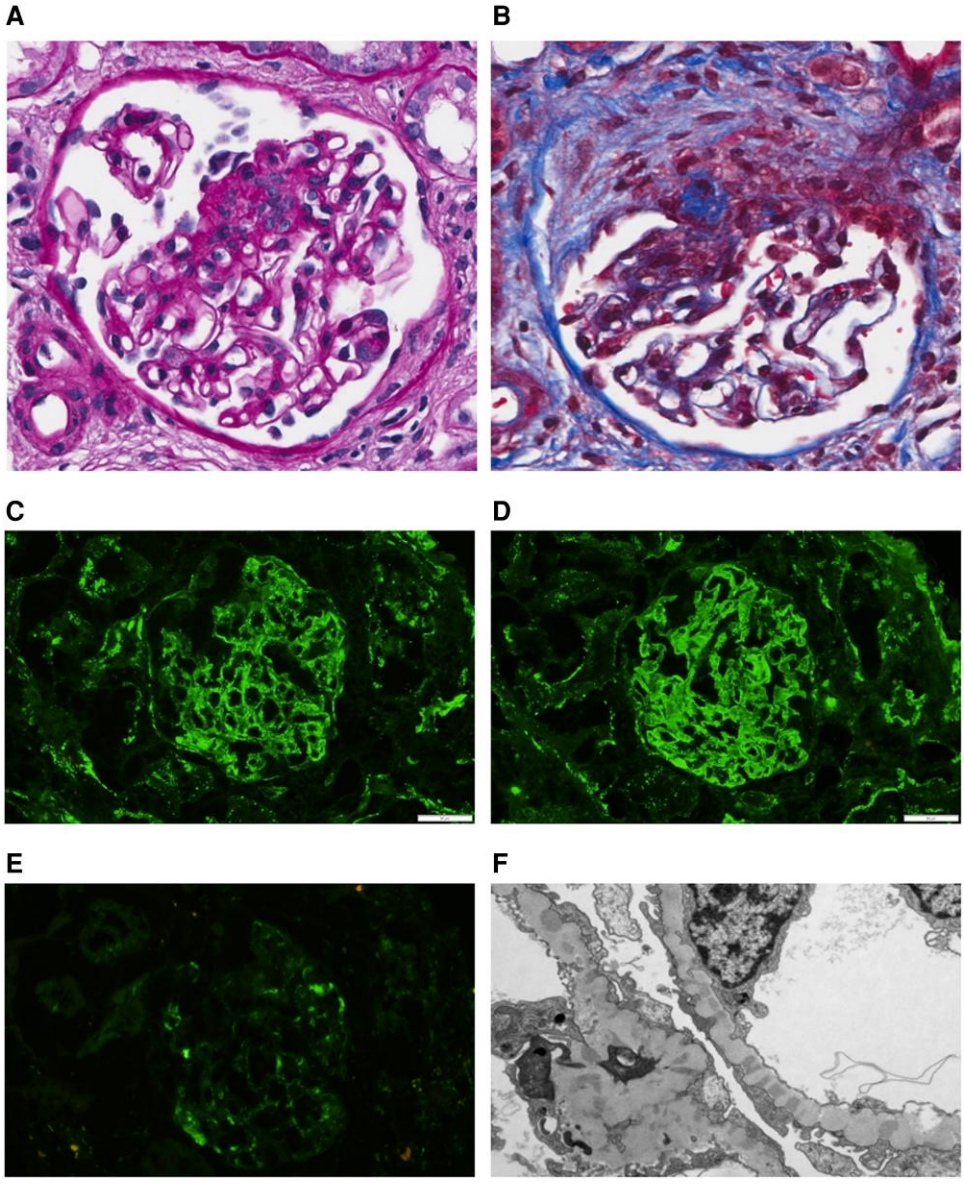

Figure 2. Histological findings consistent with severe lupus nephritis in our patient. Periodic-acid Schiff (*A*) and Masson trichrome (*B*) stains of renal biopsy of our patient prior to treatment with glucocorticoids and cyclophosphamide show hypercellularity and proliferation as well as a fibrocellular crescent involving the Bowman capsule and the glomerular tuft. Fluorescent immunohistochemical staining further demonstrates diffuse C3 (*C*) and immunoglobulin G (*D*) deposition throughout the glomerulus as well as low-intensity staining for C1q (*E*). Electron microscopy (*F*) showed intramembranous and subepithelial immune deposits with spike projections from glomerular basement membrane.

Given the hypokalemia and new-onset hypertension, we suspected itraconazole-induced pseudohyperaldosteronism driven by aberrant mineralocorticoid metabolism due to the effects of triazoles and characterized by excess mineralocorticoids in the presence of low serum renin activity and aldosterone [21, 22]. This was confirmed with an 11-deoxycortisol level of 498 ng/dL and low aldosterone (<3.0 ng/dL) and renin (<0.6 ng/dL), for which she was started on spironolactone and potassium supplementation. Urine studies revealed nephrotic-range proteinuria (spot protein to creatinine ratio, 5216 mg/g; 24-hour urine protein excretion, 5.324 g), concerning for lupus nephritis. Serum C3 and C4 were 70 and 16 mg/dL, respectively. The degree of proteinuria along with hypoalbuminemia and presence of fat lipid droplets on urine sediment examination were consistent with nephrotic syndrome.

She underwent a percutaneous renal biopsy that showed a diffuse proliferative pattern with global sclerosis in 25% of examined glomeruli associated with necrotizing and sclerosing crescents present in 7 of 8 remaining glomeruli, consistent with class IV (diffuse proliferative) and class V (membranous)

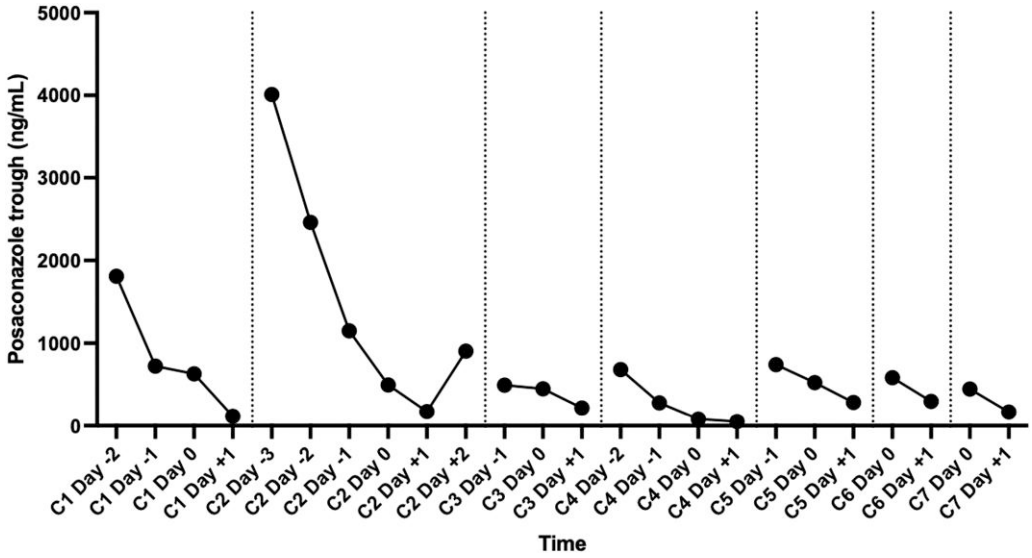

Figure 3. Posaconazole levels across the 7 cycles of cyclophosphamide administration. Represented here are posaconazole levels measured around the time of each cycle of cyclophosphamide. The number of the cyclophosphamide cycle is represented (ie, C1–C7) as well as the day relative to the day of receiving cyclophosphamide (ie, day 0 is the day of receiving each cyclophosphamide dose).

lupus nephritis (Figure 2). Given the severity and high risk for progression to end-stage renal disease, she was started on hydroxychloroquine, a 3-day intravenous pulse of methylprednisolone (1 g/day) followed by oral prednisone (40 mg/day; 0.67 mg/kg/day) with a gradual taper, and intravenous cyclophosphamide at 750 mg/m^2 dosing, which was planned monthly for 7 months. Additionally, she was started on isoniazid for LTBI and atovaquone for *Pneumocystis jirovecii* prophylaxis.

Due to concerns for the interaction between cyclophosphamide and posaconazole and given the need to treat her lupus nephritis with cyclophosphamide-based therapy, we planned to continue posaconazole but to hold it for 3 days prior to and 1 day after cyclophosphamide administration, taking into consideration the half-lives of posaconazole and cyclophosphamide being 15–25 hours [12] and 5.5 hours [23], respectively. During the 4 days that posaconazole was held, we treated the patient with micafungin (150 mg/day) to provide *Paecilomyces* coverage while receiving high-dose prednisone to minimize the risk of worsening fungal infection. With this regimen over 7 monthly cyclophosphamide cycles, she suffered no cyclophosphamide toxicity, namely myelosuppression, cardiac toxicity, hepatotoxicity, or hemorrhagic cystitis. Baseline posaconazole trough levels ranged from 1810 to 4010 ng/mL before holding posaconazole, from 81 to 583 ng/mL prior to administration of each cyclophosphamide dose, and from <50 to 296 ng/mL the day after cyclophosphamide administration when posaconazole was reinitiated (Figure 3). Her treatment prior to cycle 4 of cyclophosphamide was complicated by subjective fevers, increased fatigue, and mildly elevated transaminases (Table 1) associated with cytomegalovirus (CMV) reactivation (viral load, 6.02 $\log_{10}$ IU/mL on polymerase chain reaction [PCR] of whole blood) while receiving 15 mg of prednisone/day. She was treated with oral valganciclovir (450 mg twice/day) for 4 weeks with rapid symptom resolution. CMV PCR became undetectable when rechecked at the following cyclophosphamide cycle.

Repeat PET/CT of the chest at the time of her sixth cycle of cyclophosphamide showed improvement in the consolidation and in FDG avidity (Figure 1*B*). The urine protein to creatinine ratio improved to 818 mg/g by the seventh cycle (Figure 4), and C3 and C4 levels normalized. Serum creatinine peaked at 1.46 mg/dL (eGFR, 43 mL/minute/1.73 m^2) and improved to 0.76 (eGFR, 95 mL/minute/1.73 m^2) by the seventh cycle. Hypokalemia and hypertension resolved with treatment of lupus nephritis and a switch from itraconazole to posaconazole, allowing for discontinuation of potassium supplementation and spironolactone.

DISCUSSION

We describe a patient with severe disease processes requiring seemingly incompatible treatment regimens. Given the severe renal pathology, it was strongly felt that the patient should undergo treatment with corticosteroids and monthly cyclophosphamide [14]. The increased risk of toxicity with concomitant administration of cyclophosphamide and broad-spectrum triazoles [17–19] posed a clinical conundrum regarding the best treatment of *Paecilomyces* infection. The patient had tolerated posaconazole well and had a susceptible fungal isolate before initiation of cyclophosphamide. Alternative therapies such as amphotericin B would carry the risk of renal toxicity, and others such as olorofim have not yet been widely tested for this

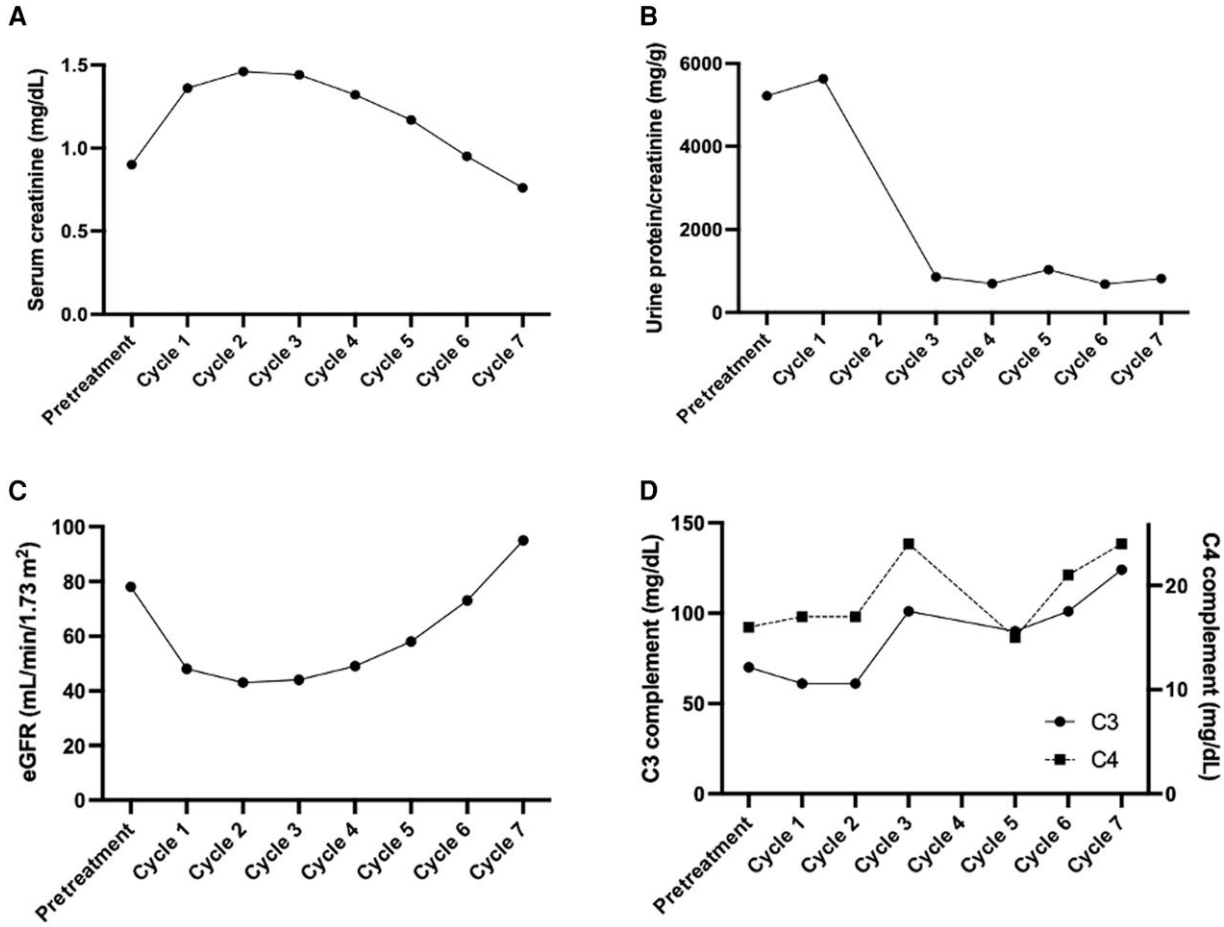

Figure 4. Improvement of lupus nephritis with cyclophosphamide-based therapy in our patient. Longitudinal evolution of the indicated laboratory values at baseline and throughout the course of 7 cycles of cyclophosphamide. Shown are urine protein/creatinine ratio (*A*), serum creatinine (*B*), glomerular filtration rate (GFR) as calculated by estimated GFR (eGFR) (*C*), and complement proteins C3 and C4 (*D*).

fungal infection. Given that this interaction is thought to be due to effects of extended-spectrum triazoles on the metabolism of cyclophosphamide resulting in delayed clearance and buildup of toxic metabolites [17, 19], we opted for a strategy of washing out posaconazole prior to administering each dose of cyclophosphamide to minimize its effects on cyclophosphamide metabolism. We describe here posaconazole treatment with brief interruptions for cyclophosphamide dosing bridged with echinocandin therapy, which was selected given minimal drug interactions, relatively low MEC value for the patient's fungal isolate, and good tolerability. It is important to note that a similar strategy of bridging with an echinocandin has shown a therapeutic benefit in other situations in which triazole therapy must be interrupted, such as during conditioning for stem cell transplantation [24]. She tolerated this regimen without apparent drug interaction–induced toxicity and showed greatly improved proteinuria and eGFR together with clinical and radiographic improvement of the fungal pneumonia. Thus, this case serves as a proof of concept that this regimen can be an effective treatment of simultaneous fungal pneumonia and lupus nephritis without severe drug-induced toxicity. The CMV viremia was managed with oral valganciclovir, resulting in resolution of viremia despite continued therapy for lupus nephritis and fungal pneumonia. This case further serves as a reminder of the unique side effects of triazole therapy, such as itraconazole/posaconazole-induced pseudohyperaldosteronism, and emphasizes the need for vigilance for this side effect in patients on prolonged courses of certain triazoles [25], whereas other triazoles seem insulated from this toxicity [26]. As nephrotic-range proteinuria has been described in posaconazole-induced pseudohyperaldosteronism [27], performing a renal biopsy was important to verify the diagnosis and severity of lupus nephritis and help guide treatment with cyclophosphamide. Also of note are the susceptibilities to the isolate of *P variotii* seen in this case—classically showing higher MICs to voriconazole indicating that it may be less effective in vivo, though there are no accepted susceptibility breakpoints for antifungals against this pathogen [1, 2, 20, 28].

The optimal length of interruption of triazole therapy for the administration of cyclophosphamide is unknown. We selected the timing presented here based on the half-lives of the medications and a desire to aggressively treat both disease states; however, it is possible that holding triazole therapy for a longer time could further reduce the risk of cyclophosphamide toxicity without jeopardizing fungal infection treatment efficacy. Importantly, the safety of this regimen may not apply to regimens of cyclophosphamide for other indications that may require higher doses or daily dosing. Differing metabolism of posaconazole among different patients may also require alterations in how long posaconazole is held. It would be advisable to measure posaconazole levels while holding the drug to ensure that levels are sufficiently low prior to administering cyclophosphamide. Furthermore, the role of bridging antifungal therapy with an echinocandin requires further study. Given the tolerability of echinocandins, this was deemed a low-risk intervention to minimize the risk of failing antifungal treatment. However, it is difficult to generalize the success of this approach to all situations given variable responses to echinocandins depending on the host [29], pathogen (such as susceptibility of even closely related fungi) [4], and pharmacokinetic factors (such as tissue-specific drug penetration) [30], so optimal therapy must be determined on a case-by-case basis. Further discussion and algorithms on adjusting antifungal therapies are detailed elsewhere [31]. Finally, a limitation in describing this case is the inability to measure serum cyclophosphamide levels.

In summary, we demonstrate that concerns regarding drug–drug interactions need not preclude concomitant aggressive treatment of lupus nephritis and fungal pneumonia providing safety monitoring measures are in place. This case report provides proof of concept for a regimen that was well tolerated and had favorable clinical outcomes.

Notes

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Patient consent. All research and care was carried out with the patient's written consent and as part of an NIH institutional review board–approved protocol (ClincalTrials.gov identifier NCT01386437). All procedures were done in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.

Potential conflicts of interest. All authors: No reported conflicts.

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