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ORIGINAL ARTICLE

Retrospective Study

Role of narrow band ultra violet radiation as an add-on therapy in peritoneal dialysis patients with refractory uremic pruritus

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Abstract

AIM

To assess the role of narrow band ultraviolet B (UVB) as a treatment option in peritoneal dialysis patients with refractory uremic pruritus.

METHODS

In this retrospective study, 29 adult patients with end stage renal failure on peritoneal dialysis, and who had refractory uremic pruritus, were given narrow band UVB radiation as an add-on therapy to standard care for a duration of 12 wk. The response to the pruritus was assessed both weekly and at the end of the study period using a visual analogue score (VAS).

RESULTS

The average VAS score at the end of the study was 3.14 ± 1.59, which was significant compared to the baseline value of 7.75 ± 1.02 ($P < 0.05$). Improvements in symptoms were noted in 19 out of 21 (90.4%) patients. However, relapse occurred in six out of the 19 patients who responded. The dropout rate was high during the study period (33.3%).

CONCLUSION

Narrow band UVB is effective as an add-on therapy in peritoneal dialysis patients with refractory uremic pruritus. However, the present regime is cumbersome and patient compliance is poor.

Key words: Narrow band ultraviolet radiation; Uremic

pruritus; Peritoneal dialysis; Visual analogue score; Retrospective study

Core tip: Uremic pruritus is a very distressing condition commonly seen in patients with advanced renal failure. Patients respond poorly to the currently available treatment regime. Narrow band ultraviolet (NUV-B) radiation is a treatment option in patients with refractory symptoms. In this study, we selected patients on peritoneal dialysis who had refractory pruritic symptoms, and used NUV-B as an add-on therapy to the standard medical care for a period of 12 wk. We found that using NUV-B improved symptoms in more than 90% of patients. However, the present regime used is not patient-friendly and compliance is poor.

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INTRODUCTION

Uremic pruritus is a very common and troublesome complication seen in patients with advanced chronic kidney disease[1-4]. The pathophysiology is complex, and many factors have been identified, including skin dryness[5,6], hyperparathyroidism[7,8], calcium phosphate deposition[9,10], imbalances between mu and kappa opioid receptors[11,12] and systemic inflammation. Anemia, inadequate dialysis, elevated serum magnesium and aluminum levels, and hepatitis C infection are also believed to have some contributing effects. However, the causes remain unexplained in many cases. There are strong associations of uremic pruritus with depressive symptoms and poor sleep quality. The pruritus is sometimes severe and refractory to treatment. Narrow band ultraviolet B (NB-UVB) phototherapy is one therapeutic option in these difficult cases. NB-UVB decreases the proinflammatory cytokine levels and induces mast cell apoptosis. In this study, we aim to investigate the role of NB-UVB as an add-on therapy to the standard treatment that is used in treating severe uremic pruritus in peritoneal dialysis patients.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Dermatology at the Jawaharlal Nehru Institute of Medical Sciences Imphal, a tertiary referral center in northeastern India. Adult end-stage renal disease patients on peritoneal dialysis with refractory uremic pruritus were included in the study. The patients were recruited from the nephrology units of three hospitals in Imphal from September 2011 to September 2017. The selected patients were referred to the Dermatology Department at the Jawaharlal Nehru Institute of Medical Sciences Imphal for NB- UVB therapy.

Inclusion criteria

In order to be eligible for inclusion in this study, patients had to be older than 18 years of age, have end-stage renal disease, be on peritoneal dialysis as their treatment modality, and have refractory uremic pruritus.

From September 2011 until September 2017, 29 patients satisfied the criteria. Uremic pruritus was defined as pruritus developing in patients with chronic kidney disease in the absence of other systemic, dermatological disorder or psychological factors. Refractory uremic pruritus was defined as uremic pruritus not that was not responsive to any of the two agents known to relieve the symptoms over a 4 wk period. These agents included topical emollients, topical capsaicin, antihistamines, pregabalin, gabapentin and tricyclic antidepressants.

Exclusion criteria

Patients with a prior history of photosensitivity, and other prior dermatological diseases that can cause pruritus, were excluded from this study.

Protocol: The patients were administered NB-UVB therapy every other day, three times per week for a total of 12 wk. They were started at a dose of 270 mJ/cm^2, and then increased by 15% at each visit. If patients had asymptomatic erythema after the session, then treatment was continued at the same dose. The dose was reduced by 15% if the patient developed erythema with minimal pain/itchiness. If the patient developed painful erythema or bullous lesions, treatment was restarted at one-third of the dosage. Phototherapy was administered using "Derma India, Chennai Lightning cubicles PUVA", which is equipped with 24 UVA lamps that emit a radiation spectrum of 320-400 nm with a maximum of 366 nm, and 24 UVB lamps that emit a radiation spectrum of 290-320 nm with a maximum of 300 nm.

The patients were allowed to continue with their previous medications/agents for uremic pruritus during the study period. A peritoneal adequacy test was performed in all patients upon entry into the study. Serum calcium, phosphate, intact parathyroid hormone, iron and hemoglobin profiles were evaluated in all patients.

A visual analogue scale (VAS) (0 = no pruritus; 10 = most severe pruritus) was used to identify the intensity of itch. VAS was measured at baseline and then weekly until the end of the 12th week. After completion of the treatment protocol, VAS was then measured monthly during the follow-up period.

Table 1 Baseline characteristics of the patients

Age (yr)	56.17 ± 15.65
Sex (male/female)	18/11
Hemoglobin (g/L)	9.99 ± 0.99
Corrected calcium (mg/dL)	8.92 ± 1.1025
Phosphate (mg/dL)	4.46 ± 1.35
Intact parathyroid hormone (pg/mL)	132.28 ± 176.63
Mean Kt/V	1.77 ± 0.11
No. of patients with weekly Kt/V > 1.7	19
Skin phototype	IV-20, V-9
Other agents used for pruritus	
Topical emollient	
Topical capsaicin	
Oral anti histaminics: Fexofenadine	
Pregabalin	
Gabapentin	
Amitryptilline	

The outcomes were grouped into the following: (1) Complete responders: defined as a VAS score of zero at the end of the study period; (2) Partial responders: defined as a VAS score between one to five at the end of treatment, and with a final VAS score less than the value at baseline; and (3) Non-responders: a VAS score greater than five at the end of the treatment period.

Relapse was defined as a VAS score greater than five after previously showing a complete or partial response.

After the completion of the treatment protocol, patients were followed-up on a monthly basis for another 6 mo. During the follow-up period, patients were assessed for relapse of the pruritus. VAS scores were recorded during these visits. A feedback form was also provided to the patient. This form allowed them to rate their experience with the treatment protocol and provide suggestions to improve their adherence.

Statistical analysis

Statistical analysis was performed using the SPSS 16 software. Continuous data were described as the mean ± SD, and categorical data by frequency and percentage. Paired *t*-tests were used to compare the mean VAS scores at baseline with those at the end of the study. A two-sided *P* score of < 0.05 was considered significant.

RESULTS

A total of 29 patients took part in this study. Seven patients dropped out during the treatment period. One patient died during this period. Baseline characteristics of the patients are shown in Table 1.

The mean age of the patients was 56 ± 15 years. The mean duration on peritoneal dialysis of these patients at the time of study was 10 ± 8 mo. The average baseline VAS for pruritus was 7.75 ± 1.02. At the end of the treatment period, the average VAS score was 3.14 ± 1.59, which was a significant drop from the baseline score ($P < 0.05$). Twenty-one patients completed the study, and 19 of them (90.4%) showed improvements in pruritus severity. Complete resolution of pruritus was noted in three patients (14.2%). Two patients (9.5%) continued to have persistent pruritus, with VAS scores greater than five (Table 2).

Follow-up data were available for 14 patients. The mean VAS score at the end of the follow-up period was 4.14 ± 2.85. Six patients relapsed with pruritus, with VAS scores greater than five. The mean time to relapse was approximately 4.2 ± 2.99 mo.

No significant adverse effects attributable to NB-UVB were identified.

DISCUSSION

Uremic Pruritus is a fairly common entity in patients with advanced renal failure, including patients on hemodialysis as well as peritoneal dialysis. In a recent study in Chinese patients, the prevalence of uremic pruritus in patients on peritoneal dialysis was approximately 62.5%[13].

The usual protocol followed in managing patient with uremic pruritus includes optimization of the dialysis dosage, optimizing treatment of hyperparathyroidism, hyperphosphatemia and anemia. Initially, patients are usually managed with emollients and topical analgesics for symptomatic measures. Many of these patients eventually require systemic medications, such as anti-histamines, pregabalin, gabapentin, and anti-depressants. Hemoperfusion has been used in combination with hemodialysis for hyperparathyroidism and pruritus in hemodialysis patients[14]. A small population of patients continue to have persistent symptoms in spite of all these measures. Phototherapy may be tried as a treatment modality in these cases.

In a small open pilot study, Ada *et al* reported a satisfactory response to NB-UVB in patients with uremic pruritus[15]. The randomized clinical study by Ko *et al*[16] showed significant improvement in the pruritus intensity, however the beneficial effect was marginal when compared to the control group that received long-wave UVA radiation.

In our study, we noted that NB-UVB phototherapy was helpful as an add-on therapy in relieving symptoms of uremic pruritus in patients on peritoneal dialysis. A previous randomized controlled trial by Ko *et al*[16] failed to show any substantial benefit compared to broadband UVA phototherapy. This lack of benefit was due to improvement in pruritus intensity in the control arm, which they attributed to the placebo effect. However, the population studied in that trial differs from that of our study. In our study, we included only patients with end-stage renal disease who were on peritoneal dialysis. Conversely, the study by Ko *et al*[16] used a mixed population of patients, including those with chronic kidney disease on conservative treatment. Only three patients in that study were on peritoneal dialysis. Another important difference from that study is the duration of the treatment period. Per our protocol, the total duration

Table 2 The baseline and weekly visual analogue assessment scores for pruritus

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Mean VAS score	7.75 ± 1.02	7.55 ± 1.02	7.48 ± 0.82	7.03 ± 0.68	6.37 ± 0.49	5.66 ± 0.55	5.53 ± 0.64	5.20 ± 0.70	4.87 ± 0.74	4.60 ± 0.72	3.04 ± 1.32	3.42± 1.63	3.14 ± 1.59
No. of patients	29	29	29	29	27	27	26	25	24	23	22	21	21

VAS: Visual analogue score.

of therapy was 12 wk compared to the six week time-span used in the randomized trial. The extended duration of our treatment is based on our preliminary experience with such patients, where we noted a more significant improvement in symptoms when they received a more prolonged course of treatment.

The pathophysiology involved in uremic pruritus is very complex and multifactorial. Multiple hypotheses have been proposed, including the potential involvement of anemia, xerosis, hyperparathyroidism, hyperphosphatemia, inadequate dialysis, imbalance of opioid receptors, and inflammation. Some of the factors that contribute to pruritus in non-dialysis patients may not be applicable in patients who are already on peritoneal dialysis. The response of uremic pruritus to phototherapy may differ in the peritoneal dialysis population when compared to patients on hemodialysis. The beneficial effects of NB-UVB is believed to be attributable to the induction of mast cell apoptosis and the reduction in proinflammatory cytokine levels[17].

In our study, the mean hemoglobin levels (9.99 ± 0.9) are very near the target set by KDIGO[18]. The serum phosphate levels (mean value 4.44 mg/dL) and intact parathyroid levels (mean value 132.28 pg/mL) were also reasonable for patients on dialysis. Nineteen out of the 21 patients who completed the study had adequate small solute clearance (weekly kt/v > 1.7), suggesting that factors other than inadequate dialysis played a significant role in the pathogenesis of uremic pruritus in our patients.

We noted that using NB-UVB as an add-on therapy was effective in our patients. The mean VAS score improved from a baseline score of 7.75 ± 1.02 to 3.14 ± 1.59 by the end of therapy. Complete resolution of pruritus was noted in three patients (14.2%). In two patients (9.5%), no significant improvements were noted. Six of the patients who showed an improvement in pruritus ultimately relapsed (31.5%).

The beneficial effects of the phototherapy session set in by the 3rd week, and the effect became more pronounced after the end of the 7th week. The mean VAS score at the end of six weeks was 5.53 ± 0.64, which means that many of these patients would have been classified as non-responders if they had received the 6 wk protocol, as in the previous randomized trial. The mean VAS score at the end of the 6 mo follow-up was 4.14 ± 2.85, which was significantly lower than the baseline VAS score ($P < 0.001$).

Our study is limited by its retrospective nature. Although the population studied here is uniform, it is also small. We noted that it was difficult for the patients to strictly abide by the three times per wk for 12 wk UVB protocol. Upon reviewing the feedback forms, we realized that our patients found the treatment regime to be cumbersome, and many were not willing to enroll in a repeat course of such treatment sessions in the future. This was in spite of the short duration of each session, usually lasting less than two to 3 min. Many of the patients found the frequent visits to the hospital to be very inconvenient. Transportation was also a big hindrance, as many of these patients cannot drive and thus arranging logistical support to bring them to the hospital three times a wk for 12 wk becomes an issue. It is noted that the duration of the overall treatment protocol was longer compared with previous studies. As such, one might consider a slightly shorter duration of NB-UVB treatment (*e.g.,* twice per week for eight to 10 wk, or three times per week for 8 wk).

Many questions still remained unanswered at the end of this study. The treatment, even if effective, does not offer long-term protection. Relapse occured in nearly a third of the patients. The optimal treatment duration and frequencies of the session are not known. As such, we need to come up with a large well-designed randomized controlled trial comparing different treatment regimes in order to come up with the most effective yet acceptable regime.

In conclusion, using NB-UVB as an add-on therapy to standard agents in refractory uremic pruritus on peritoneal dialysis is effective in reducing the intensity of itching. However, there is a chance of relapse after discontinuation of the phototherapy. The 12 wk treatment regime used in this study is cumbersome and patient acceptance is poor.

ARTICLE HIGHLIGHTS

Research background

Uremic pruritus is a common and troublesome entity in patients on peritoneal dialysis. The presence of pruritus affects both sleep quality and overall lifestyle, which can lead to depressive symptoms and mood disorders. In patients with difficult-to-treat pruritus, narrow band ultraviolet B (NB-UVB) can be tried as a treatment option. There is only one randomized controlled trial that has compared the role of NB-UVB in uremic pruritus. There is very limited data regarding the use of NB-UVB in the peritoneal dialysis population. There is therefore an urgent need to identify the effectiveness of such a treatment modality in the peritoneal dialysis population.

Research motivation

With the limited data available, there is no clear-cut consensus regarding the role of NB-UVB in peritoneal dialysis patients who have severe pruritus. The most effective and optimal duration of treatment is also not clear. A previous randomized trial had used a course of three times a week for 6 wk. However, that study mixed in a population of chronic kidney disease patients and also included patients on hemodialysis, peritoneal dialysis, as well as patients who were treated conservatively and had not been initiated on dialysis. There were only three patients in this study who were on peritoneal dialysis, so the results therefore cannot be extrapolated to the peritoneal dialysis population. In this study, we selected a homogenous population of patients with end-stage renal disease who were on peritoneal dialysis with severe uremic pruritus, and used NB-UVB as an add-on therapy to the standard treatment.

Research objectives

The purpose of our study was to assess the effectiveness of NB-UVB as an add-on therapy to standard treatment in peritoneal dialysis patients with refractory uremic pruritus. We included a follow-up 6 mo post-treatment completion to assess for relapse. Patients were also given a feedback form to highlight their experience with the treatment protocol and solicit their suggestions to improve the quality of treatment.

Research methods

This is a retrospective study where peritoneal dialysis patients with refractory uremic pruritus were put on a 12 wk course of NB-UVB, in addition to their standard treatment. We used visual analogue scale (VAS) to record the intensity of pruritus, which was measured during each visit. After the completion of their treatment protocol, patients were followed-up on a monthly basis for six months, and their VAS scores were measured during these visits. The patient feedback forms were also collected during these follow-up visits.

Research results

In this study, we noted that the mean VAS score improved from a baseline of 7.75 ± 1.02 to 3.14 ± 1.59 by the end of treatment. Nineteen out of the 21 patients who completed the study had improvement in symptoms. In three patients (14.2%), complete resolution of pruritus was noted. Two patients (9.5%) continued to have persistent pruritus, with VAS scores greater than five. Six (31.5%) of those patients who showed improvement in pruritus ultimately relapsed. The mean VAS score at the end of the 6 mo follow-up was 4.14 ± 2.85, which was significantly lower than the baseline VAS score ($P < 0.001$).

Research conclusion

In this study, we found that NB-UVB therapy is effective as an add-on therapy in difficult-to-treat patients with uremic pruritus in the peritoneal dialysis population. In our study, we used a 12 wk treatment protocol that showed effective results. We noted that the response at 6 wk was suboptimal, and many of our patients would have been classified as non-responders if our treatment was confined to 6 wk period. However, patient compliance was poor, and the frequent visits to the hospital for treatment became an issue when we used the 12 wk regime. We therefore need to come up with an effective treatment regime that will also be acceptable to patients.

Research perspectives

Future studies should try alternative treatment regimes, such as two times per wk for 10 wk, or three times per wk for 8 wk.

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CASE REPORT

Case of human immunodeficiency virus infection presenting as a tip variant of focal segmental glomerulosclerosis: A case report and review of the literature

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Author contributions: All of the authors worked as clinicians for this patient; Goto T and Ohashi N wrote the paper; Fujigaki Y, Shimizu A and Yasuda H reviewed the manuscript.

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Abstract

The incidence of the collapsing variant of focal segmental glomerulosclerosis (FSGS) as a human immunodeficiency virus (HIV)-associated nephropathy has reduced since the introduction of antiretroviral therapy (ART). However, the incidence of other variants of FSGS, except for the collapsing variant, is increasing, and its therapeutic strategies remain uncertain. A 60-year-old HIV infected man in remission with ART was admitted for progressive renal insufficiency and nephrotic-ranged proteinuria. Renal biopsy revealed a tip variant of FSGS and his clinical manifestations resolved with corticosteroid therapy. HIV infected patients might develop non-collapsing FSGS, including tip variant of FSGS and corticosteroid therapy might be effective for them. A renal biopsy might be essential to determine the renal histology and to decide on corticosteroid therapy.

Key words: Focal segmental glomerulosclerosis; Tip variant; Antiretroviral therapy; Corticosteroid therapy;

Human immunodeficiency virus

Core tip: Collapsing variant of focal segmental glomerulosclerosis (FSGS) is the most common kidney disease in human immunodeficiency virus (HIV) infected patients. However, the incidence has reduced since the introduction of antiretroviral therapy (ART). Although the incidence of other variants of FSGS, except for the collapsing variant, is increasing, the tip variant of FSGS has been rarely reported. Therefore, we report an HIV infected patient under remission with ART, who presented with a rare tip variant of FSGS, which resolved with corticosteroid therapy. We suggest a renal biopsy might be essential to determine the renal histology and to decide on corticosteroid therapy.

Goto D, Ohashi N, Takeda A, Fujigaki Y, Shimizu A, Yasuda H, Ohishi K. Case of human immunodeficiency virus infection presenting as a tip variant of focal segmental glomerulosclerosis: A case report and review of the literature. *World J Nephrol* 2018; 7(4): 90-95 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i4/90.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i4.90

INTRODUCTION

Human immunodeficiency virus (HIV) infection as a cause of various kidney diseases is well known. The collapsing variant of focal segmental glomerulosclerosis (FSGS), as an HIV-associated nephropathy (HIVAN), is one of the most frequently occurring kidney diseases[1]. HIVAN was first reported by Rao *et al*[2] in 1984. It is characterized by tubular abnormalities that include cellular degeneration and necrosis as well as cystic dilatation and interstitial changes that are edematous and often infiltrated by lymphocytes, in addition to the collapsing variant of FSGS[2].

Antiretroviral therapy (ART) is effective for preserving renal function and reversing HIVAN[3]. It is reported that the use of ART slows the progression to renal replacement therapy in patients with HIVAN[4]. However, ART has no beneficial effect on the renal function in patients with lesions other than HIVAN, including the tip variant of FSGS[4]. HIV-immune-complex kidney disease (HIVICK), thrombotic microangiopathy, and nephrotoxicity caused by ART are the other types of renal damage associated with HIV infection[3]. Although the occurrence of other variants of FSGS, except the collapsing variant, is increasing[5], the tip variant of FSGS is still a rare kidney disease in HIV infected patients[6]. We report here, a rare case of HIV associated nephrotic syndrome caused by the tip variant of FSGS, which was resolved with corticosteroid therapy.

CASE REPORT

A 60-year-old HIV positive Asian male was treated with ART (abacavir, atazanavir, and lamivudine) since the early 2000s. He had been HIV RNA negative since September 2010. There were no urinary abnormalities and his serum creatinine (sCr) level was within normal limits (sCr 0.72 mg/dL) in June 2015. However, he developed edema of the lower limbs beginning in the middle of June 2015 and gained 6 kg in two weeks. No symptoms of heart failure were found during the clinical course. His sCr level increased to 1.0 mg/dL. Atazanavir was changed to dolutegravir at the beginning of July 2015, due to suspicion of atazanavir-induced nephropathy. However, his sCr further increased to 1.99 mg/dL. Hypoalbuminemia (0.8 g/dL) and massive proteinuria (16.96 g/gCr) were observed in late July 2015 at which time he was admitted to our institute.

He had no other significant past history except for the HIV infection. He was on abacavir, lamivudine, and dolutegravir as ART, and azosemid to reduce the edema of the lower limbs. Physical examination on admission was as follows: Height 166 cm, weight 86.2 kg, body mass index (BMI) 31.3 kg/m^2, body temperature 36.3 ℃, blood pressure 114/89 mmHg, and regular pulse rate 101 beats/min. Extremities had remarkable pitting edema. Laboratory investigations were shown in Table 1.

A renal biopsy was performed in late July 2015. The light microscopic findings revealed that 34 out of 35 glomeruli showed minor glomerular abnormalities without glomerular hyperfiltration. In addition, changes of the glomerular capillaries, such as spike formation and bubbling appearance, or glomerular nodular lesions were not found. However, one glomerulus showed epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet was observed. No collapse of the glomerular tuft was seen. Although diffuse tubular atrophy and interstitial fibrosis were seen, infiltration of inflammatory cells was sparse and microcystic tubular dilatation associated with HIVAN was absent (Figure 1). Immunofluorescent microscopic examination showed the absence of immunoglobulins and complements (data not shown). Electron microscopy revealed a wide range of foot process effacement. No thickness of glomerular basement membrane was observed. Moreover, no tubulo-reticular inclusions in the glomerular endothelium were found and electron-dense deposits (EDDs) were absent (Figure 2). A diagnosis of tip variant of FSGS was made.

Following renal biopsy, corticosteroid therapy (prednisolone 50 mg/d) and angiotensin Ⅱ receptor blocker (ARB) were administered to reduce the proteinuria. Three weeks later, proteinuria was absent and the levels of sCr and urinary β2-microglobulin decreased from 1.99 mg/dL to 0.99 mg/dL, and 65500 μg/L to 346 μg/L, respectively. Thereafter, the dose of prednisolone was tapered and there was no recurrence of proteinuria

Table 1 Laboratory data at the time of administration

Hematology		Blood chemistry		Immunology		Urinalysis	
WBC	7720/μL	Na	133 mEq/L	CRP	0.27 mg/dL	Protein	11.28 g/24 h
CD4	549/μL	K	4.1 mEq/L	IgG	426 mg/dL	Sugar	3+
RBC	567 × 10^4/μL	Cl	106 mEq/L	IgA	293 mg/dL	Occult blood	3+
Hb	18.9 g/dL	Ca	7.2 mg/dL	IgM	83 mg/dL	Urinary RBC	5-9/HPF
Hct	53.20%	Pi	2.6 mg/dL	CH50	48.7 U/mL	β2MG	65500 g/L
Plt	42.5 × 10^4/μL	BUN	20.1 mg/dL	C3	159 mg/dL	NAG	173.2 IU/L
		sCr	1.99 mg/dL	C4	42 mg/dL	Crystal	(-)
		UA	4.4 mg/dL	ANA	40 ×		
		LDH	243 IU/L	MPO-ANCA	< 1.0 U/mL		
		AST	23 IU/L	PR3-ANCA	< 1.0 U/mL		
		ALT	20 IU/L	anti-GBM Ab	< 2.0 U/mL		
		TP	3.9 g/dL				
		Alb	0.8 g/dL				
		LDL-cho	418 mg/dL				
		BS	121 mg/dL				
		HIV RNA	(-)				
		HBS Ag	(-)				
		HCV Ab	(-)				

CD: Cluster of differentiation; BUN: Blood urea nitrogen; sCr: Serum creatinine; UA: Uric acid; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDL-cho: Low-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; HBS Ag: Hepatitis B virus surface antigen; HCV Ab: Hepatitis C virus antibody; CRP: C-reactive protein; CH50: Total complement activity; ANA: Anti-nuclear antibody; MPO-ANCA: Myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA: Proteinase 3-antineutrophil cytoplasmic antibody; Anti-GBM ab: Anti-glomerular basement membrane antibody; HPF: High power field; β2MG: β2 microglobulin; NAG: N-acetylglucosaminidase.

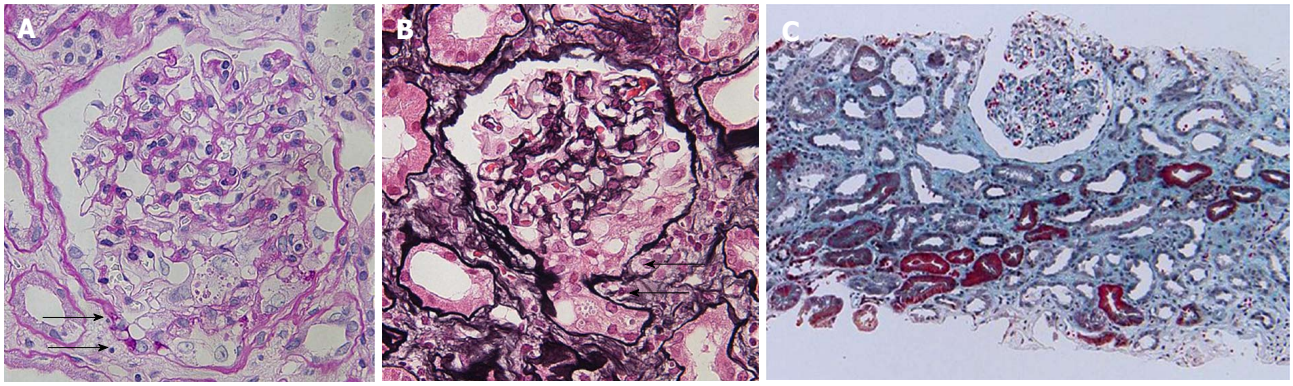

Figure 1 The results of light microscopy. A and B: The glomerulus shows epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet is observed (arrows). No collapse of the glomerular tufts associated with human immunodeficiency virus-associated nephropathy (HIVAN) is seen (A: Periodic acid-Schiff stain: Original magnification 400 ×; B: Periodic acid-methenamine-silver-HE stain: Original magnification 400 ×); C: Diffuse tubular atrophy and interstitial fibrosis are seen. However, infiltration of the inflammatory cells is sparse and microcystic tubular dilatation associated with HIVAN is absent (Masson's trichrome stain: Original magnification 100 ×).

(Figure 3).

DISCUSSION

An HIV infected patient in remission with ART, was diagnosed with the tip variant of FSGS. Steroid treatment corrected the renal dysfunction and nephrotic-ranged proteinuria.

Although it is generally considered that HIV infection of the renal cells and HIV viral proteins play an important role in the occurrence and the progression of HIVAN[3], HIV RNA was negative in this case. It is known that HIV patients may develop non-collapsing FSGS, even when HIV mRNA levels are negative. Lescure *et al*[5] reported that FSGS was the primary diagnosis in 21 of the 32 patients (65% of total, HIVAN: 6 patients, non-collapsing FSGS: 15 patients) who underwent a renal biopsy from 2004 to 2007 when ART was the standard therapy for HIVAN. In addition, non-collapsing FSGS accounted for 15 of 26 patients (58%) who underwent renal biopsy for causes other than HIVAN[5]. The high incidence of non-collapsing FSGS in this study may be due to 66% of the included patients identified their race as black. It is known that patients of African descent are susceptible to genetic mutations of APOL1, which is associated with the development of FSGS[7]. Though the incidence of biopsy-proven idiopathic FSGS was reported to be 49% in black patients[8]. Thus, the prevalence of non-collapsing FSGS in patients with HIV infection seemed to be higher compared to that in black patients without HIV infection.

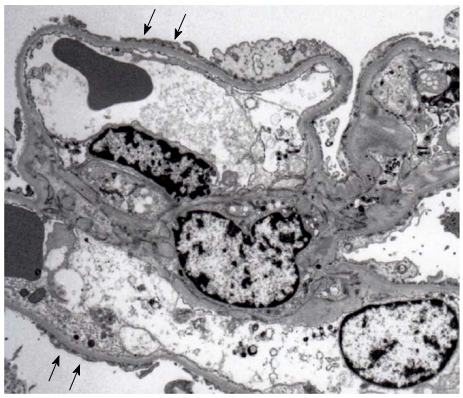

Figure 2 The results of electron microscopy. Electron microscopy reveals a wide range of foot process effacement (arrows). No tubulo-reticular inclusions in the glomerular endothelium are seen and electron-dense deposits are absent (original magnification: 3000 ×).

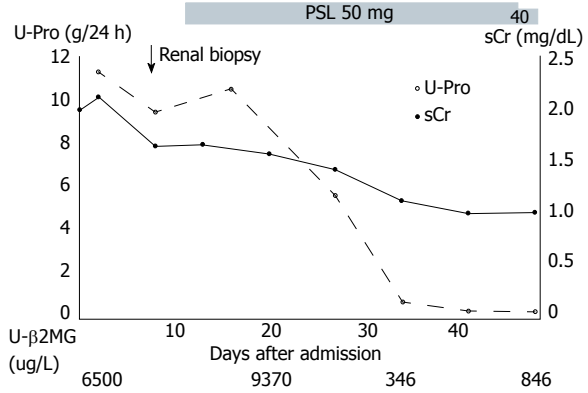

Figure 3 Clinical course after admission. The solid line with closed circles indicates serum creatinine (sCr) levels, and the dashed line with open circles indicates daily urinary protein (U-Pro) excretion levels. PSL: Prednisolone, U-β2MG; Urinary β2-microglobulin.

Moreover, the patients with HIV infection might be susceptible not only to HIVAN but also to another variant of FSGS.

The tip variant of FSGS is a rare kidney disease in HIV infected patients. Meehan *et al* reported that only one of twenty-six patients developed a tip variant in a cohort of 46 HIV positive patients[6]. Howie and Breer defined the term glomerular tip lesion (GTL) as hypercellularity at the tubular pole in nephrotic patients for the first time[9]. Since GTLs are observed in some glomerular disorders such as membranous nephropathy, IgA nephropathy, or diabetic nephropathy, it is possible that GTLs are interpreted as nonspecific renal pathological findings[10]. However, since the rate of chronic kidney diseases and end-stage renal failure is higher in patients with GTLs compared to patients with minimal change nephrotic syndrome, GTLs are considered as a variant of FSGS[11]. However, the tip variant of FSGS exhibits unique characteristics among idiopathic FSGS. Several reports mention that the levels of interstitial fibrosis, global sclerosis, and glomeruli with segmental lesions were lower in the tip variant of FSGS and the rate of complete remission of the nephrotic syndrome is higher than that in not otherwise specified (NOS) variants of FSGS[11]. It is difficult to deny that GTLs were completely caused by other diseases. However, in this case no significant findings except for segmental lesions in one glomerulus were found in the light microscopic findings. The absence of immunoglobulins and complements by immunofluorescent microscopic examination and the absence of the thickening of the glomerular basement membrane and EDDs by electron microscopic examination excluded that the GTLs were caused by other diseases and confirmed the diagnosis of the tip variant of FSGS.

Because this patient was remarkably obese (BMI: 31.3 kg/m^2), obesity-associated FSGS was suspected as a differential diagnosis. However, this patient's clinical features were considerably different than those of obesity-associated FSGS based on the following evidence: (1) Although obesity was not improved, urinary protein levels were dramatically decreased by steroid treatment; and (2) Praga *et al*[12] reported that the levels of proteinuria in obesity-associated FSGS are lower and that the incidences of hypoalbuminemia and edema are less frequent than in patients with idiopathic FSGS. In addition, they indicated that glomerular hyperfiltration is more frequently found in renal biopsy specimens of patients with obesity-associated FSGS than in renal biopsy specimens of patients with idiopathic FSGS. Therefore, this case was unlikely to be of obesity-associated FSGS.

It could not be completely denied that this was a case of a patient with HIV infection and the tip variant of FSGS. However, Lescure *et al*[5] indicated that HIVAN decreased from 75% in 1995-2000 to 29% in 2004-2007 because of the introduction of ART, and that FSGS other than HIVAN conversely increased from 11.1% in 1995-2000 to 46.9% in the 2004-2007. The incidence of FSGS with HIV infection in both periods is much higher (86.1% in 1995-2000 and 75.9% in 2004-2007) than that of black patients without HIV infection (49%)[8]. Those results indicated that HIV infection is associated with the FSGS pathogenesis with or without the presence of HIV RNA. Additionally, immunodeficiency and dysregulation of immunoglobulin synthetic responses and T-cell function, which can lead to pathogenesis of kidney diseases, are increased in HIV infected patients[13]. It is likely that the corticosteroid therapy corrected the dysregulation of the immune system caused by the HIV infection in this tip variant of FSGS. However, the pathogenesis of FSGS without HIV RNA in HIV infected patients who were effectively treated with ART should be clarified.

At first, atazanavir-induced progressive renal insufficiency and nephrotic-ranged proteinuria were suspected. However, these did not improve after the discontinuation of atazanavir. Moreover, to the best of our knowledge, atazanavir-induced tip variant of FSGS has yet to be reported in literature. Therefore, we believe that atazanavir did not cause the massive progressive renal

insufficiency and nephrotic-ranged proteinuria.

In this case, the level of urinary β2MG was markedly elevated at the time of admission and rapidly decreased with corticosteroid therapy. Exposure to tenofovir, indinavir, and atazanavir has been reportedly associated with a higher incidence of chronic kidney disease[14]. Atazanavir is known to cause crystalluria and urolithiasis[15]. In this case, the patient began receiving dolutegravir after it was suspected that the atazanavir was inducing nephropathy. Fujigaki *et al*[16] reported proximal tubular injuries in adults with minimal change nephrotic syndrome, which was probably due to massive proteinuria. As previously described, early discontinuation of atazanavir, as well as early remission of massive proteinuria, may improve the tubulointerstitial damage and rapidly decrease urinary β2MG excretion levels, as seen in this case.

In conclusion, this was a rare case of a patient in remission from HIV who presented with the tip variant of FSGS. Since the tip variant of FSGS can occur in HIV patients in remission with ART, a renal biopsy might be essential to determine the renal histology, and to decide on corticosteroid therapy. Further research with a larger sample size of patients is necessary to understand the mechanisms and efficacy of corticosteroid therapy for the tip variant of FSGS in HIV-infected patients.

ARTICLE HIGHLIGHTS

Case characteristics

We reported a human immunodeficiency virus (HIV) infected patient in remission with antiretroviral therapy (ART), who presented with a rare tip variant of focal segmental glomerulosclerosis (FSGS), which resolved with corticosteroid therapy.

Clinical diagnosis

We diagnosed the patient as a case of HIV infection presenting as a tip variant of FSGS.

Differential diagnosis

HIV-associated nephropathy (HIVAN) or other causes of FSGS have to be differentiated because therapeutic strategies (ART or steroids) are different.

Laboratory diagnosis

Whether HIV RNA levels are positive or negative are important.

Pathological diagnosis

Tip variant of FSGS is needed to diagnose that more than one glomerulus show epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet is observed in renal biopsy specimen.

Treatment

Steroid therapy is considered to administer to other causes of FSGS except for HIVAN including the tip variant.

Related reports

Lescure *et al* is important for the readers to understand the changes of HIV-associated kidney glomerular diseases with time and ART.

Term explanation

Tip variant is one of the diagnoses in the Columbia classification of FSGS and is explained as follows: More than one glomerulus shows epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet is observed in renal biopsy.

Experiences and lessons

When renal damage is caused in HIV-infected patients, a renal biopsy may be essential to determine the renal histology and to decide on corticosteroid therapy.

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