Pseudoporphyria Associated with Chronic Renal Failure: The Outcome from Oral N-Acetylcysteine Treatment in Three Cases

Kronik Böbrek Yetmezliği ile İlişkili Psödoporfiri: Üç Olguda Oral N-Asetilsistein Tedavisinin Sonuçları

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ABSTRACT Pseudoporphyria is a rare and acquired bullous disorder with clinical and histopathological features identical to porphyria cutanea tarda, despite a normal porphyrin metabolism. It is associated with chronic renal failure, excessive sun exposure and various medications. There is no specific treatment for pseudoporphyria, but sun protection and discontinuation of the offending drugs may provide some benefit. Oral N-acetylcysteine has recently been reported as an effective treatment option in five cases in the literature. Here, we described our experience with N-acetylcysteine treatment in three patients with pseudoporphyria due to chronic renal failure.

Key Words: Kidney failure, chronic; therapy; acetylcysteine

ÖZET Psödoporfiri, klinik ve histopatolojik olarak porfiriya kutanea tardaya benzeyen, ancak porfirin metabolizmasının normal olduğu, nadir görülen, edinsel, büllöz bir deri hastalığıdır. Kronik böbrek yetmezliği, aşırı güneş maruziyeti ve çeşitli ilaçlarla ilişkilendirilmektedir. Psödoporfirinin spesifik bir tedavisi olmamakla birlikte, güneşten korunma ve sorumlu ilacın kesilmesi kısmi yarar sağlayabilmektedir. Literatürde, yakın zamanda beş olguda oral N-asetilsistein'in etkili bir tedavi seçeneği olabileceği bildirilmiştir. Burada kronik böbrek yetmezliği zemininde gelişen üç psödoporfiri olgusunda oral N-asetilsistein tedavi deneyimimizi sunmaktayız.

Anahtar Kelimeler: Böbrek yetmezliği, kronik; tedavi; asetilsistein

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Pseudoporphyria is a rare and acquired bullous disorder with clinical and histopathological features similar to those of porphyria cutanea tarda (PCT) despite a normal porphyrin metabolism. It is associated with chronic renal failure, excessive sun exposure and numerous medications such as furosemide, hydrochlorothiazide, tetracycline and naproxen.[1] So far, there has been no specific treatment for pseudoporphyria, although sun protection and discontinuation of the offending drugs may provide some benefit.

Oral *N*-acetylcysteine has recently been reported as an effective treatment option in five cases.[2-6] This paper was aimed to share our experience on and present outcome of *N*-acetylcysteine treatment option in three pseudoporphyria patients associated with chronic renal failure.

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CASE REPORTS

CASE 1

A 38-year-old woman with chronic renal failure undergoing hemodialysis 3 times/week had a 2-month history of multiple tense blisters and erosions with crusting and atrophic scars on her face and dorsum of the hands (Figure 1). Her medical history also disclosed chronic hepatitis C infection. Liver function tests and serum ferritin levels were normal.

CASE 2

A 56-year-old woman presented a 2-week history of multiple tense blisters, eroded and crusted areas on her face and dorsum of the hands (Figure 2). She had been undergoing hemodialysis 3 times/week for chronic renal failure for 7 years.

CASE 3

A 72-year-old woman presented an 18-month history of multiple hemorrhagic blisters on her abdomen (Figure 3) and dorsum of the hands. She had been on hemodialysis 3 times/week for chronic renal failure for one year. Her medications included hydrochlorothiazide.

Histopathological examinations revealed subepidermal bullae in all patients (Figure 4). Direct immunofluorescence studies of the perilesional

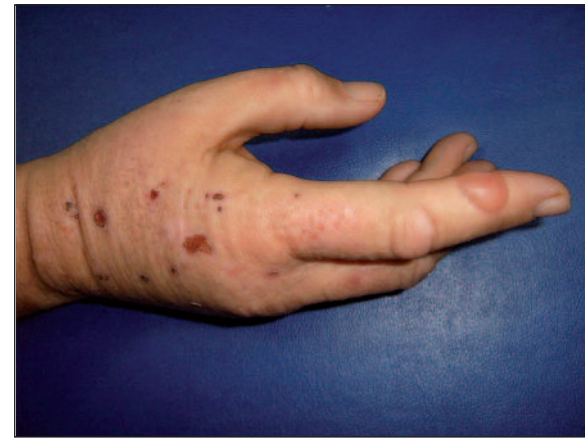

FIGURE 2: Case 2: Multiple tense blisters, eroded and crusted areas on the hands.
(See for colored from http://tipbilimleri.turkiyeklinikleri.com/)

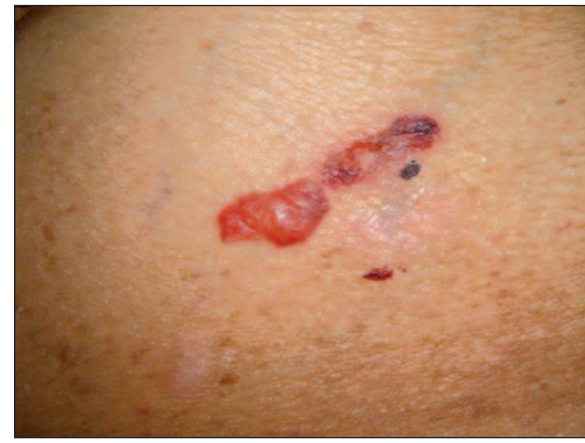

FIGURE 3: Case 3: Multiple hemorrhagic blisters on the abdomen.
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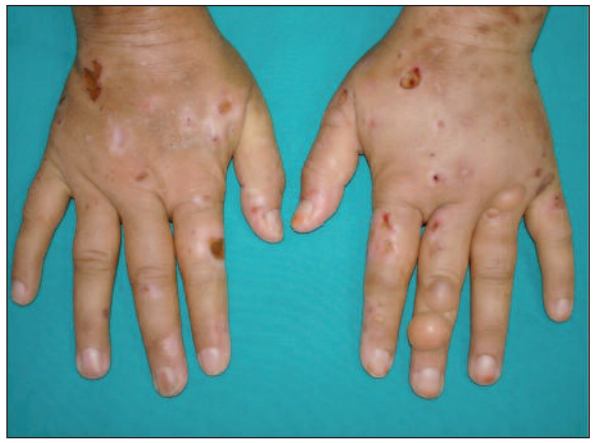

FIGURE 1: Case 1: Multiple tense blisters and erosions with crusting and atrophic scars on the dorsum of the hands.
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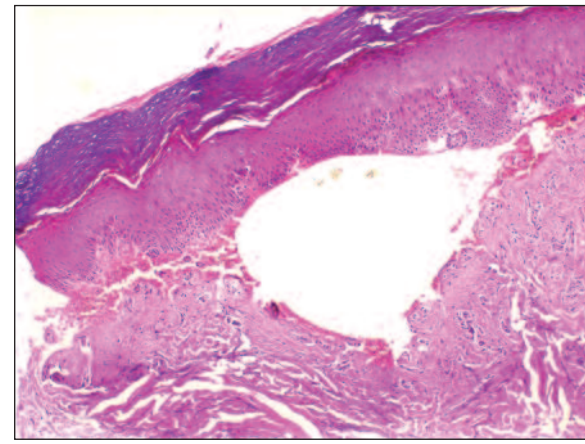

FIGURE 4: Case 2: Histopatology of a blister from the dorsum of the hand showing subepidermal bullae (H&E, x10).
(See for colored from http://tipbilimleri.turkiyeklinikleri.com/)

skin were negative. Urine uroporphyrin levels were within normal limits (normal, <25 μg/L). Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with Because of kidney failure, the patients had not been able to excrete enough urine in the mornings; thus the urine test could be performed with normal.

On the basis of clinicopathological correlation and porphyrin data, all three patients were diagnosed with pseudoporphyria. Hydrochlorothiazide treatment was stopped in the case 3 but its cessation failed to relieve the lesions. Oral *N*-acetylcysteine (1,200 mg/day) treatment was initiated in addition to strict sun protection by wearing protective clothes, using broad-spectrum sun protection factor 30 sunscreen and avoiding direct sun exposure during day time. One month after changing the treatment, new bullae development had stopped in the cases 1 and 3 and no further lesions occurred during a 6-month follow-up. However, new bullae continued to develop in the case 2 despite increasing the dose of *N*-acetylcysteine by half (1.800 mg/d). None of the patients complained about any side effects of oral administration of *N*-acetylcysteine.

DISCUSSION

Porphyrias are characterized by abnormalities in the heme biosynthetic pathway. Porphyria cutanea tarda is a photo-induced blistering disorder caused by an inherited or acquired deficiency of uroporphyrinogen decarboxylase, leading to accumulation of porphyrins mainly in urine but also in stool and plasma. Patients with PCT present with skin fragility and bulla formation which heal with milia and scarring, most frequently on photo exposed skin. Facial hypertrichosis and hyperpigmentation are common. Histopathologically, subepidermal bullae with classic festooning of the dermal papillae, thickening of the dermal vessel walls and dermal sclerosis are observed.[7,8]

Pseudoporphyria is clinically and histologically similar to PCT, but typically lacks the biochemical abnormalities. Both pseudoporphyria and PCT may occur with increased frequency among patients with chronic renal failure undergoing hemodialysis.[9] It is important to make a complete porphyrin examination of urine, plasma and stool to distinguish pseudoporphyria from PCT. However, this can be challenging especially in the setting of renal failure and hemodialysis. Usually a morning urine sample of 20 ml is analyzed for porphyrins, but due to severe renal failure and anuria, as in our cases, enough amount of morning urine sample may not be collected. There is also disagreement on whether pseudoporphyria has a completely normal porphyrin profile or may have elevated plasma porphyrins in the setting of renal failure.[10-13] Plasma porphyrins may increase because of impaired excretion of these molecules and inefficient clearance by dialysis since porphyrins have too high molecular weight to be cleared by the hemodialysis membrane. Thus, it is better to investigate patients' porphyrin profile by fractionation of fecal porphyrins.[13] However, we were unable to perform fecal porphyrin analysis in our patients.

The exact pathogenesis of pseudoporphyria associated with chronic renal failure is not fully clarified. Dermal microangiopathic changes and decreased oxygenation during hemodialysis may facilitate frictional blistering.[14] Hemodialysis patients are prone to oxidative stress and have decreased levels of glutathione which is considered to be one of the most important antioxidant systems.[15-17] Other proposed factors triggering pseudoporphyria associated with hemodialysis include various drugs (diuretics, aluminum hydroxide, nifedipine, erytropoetin) hemosiderosis, and hepatitis C infection.[1] One of our cases also had a chronic hepatitis C infection. It is well-known that chronic hepatitis C infection is most frequently associated with PCT.[7,18] Hepatitis C infection may trigger symptomatic PCT in genetically predisposed patients.[19] Porphyrin analysis excluded a diagnosis of PCT in our patient. We thought that hydrochlorothiazide treatment was a possible triggering factor in another patient. However, it seems unlikely that this drug was responsible alone for the patient's condition because its cessation failed to clear the skin lesions.

Oral *N*-acetylcysteine, a synthetic precursor of reduced glutathione (GSH), is a thiol-containing compound that facilitates intracellular biosynthesis of glutathione particularly in increased oxidative stress.[20] It can prevent increased oxidative stress following administration of radiocontrast agents and therefore has become widely used to prevent contrast-induced nephropathy. Meanwhile, *N*-acetylcysteine supplementation has been shown to be a promising therapy for oxidative stres and related complications including cardiovascular events in hemodialysis patients.[21,22] On the basis of its antioxidant properties and its ability to replenish depleted glutathione levels , oral *N*-acetylcysteine has recently been used to treat 6 cases with hemodialysis-associated pseudoporphyria, and has shown beneficial effect in five of them.[2-6] Switch from low-flux to high-flux membrane hemodialysis has also been used in combination with *N*-acetylcysteine in order to prevent recurrence of blistering after discontinuation of the drug in one of those cases.[4] We describe our experience with oral *N*-acetylcysteine in further 3 cases of hemodialysis-associated pseudoporphyria. After 1-month of this treatment, new bullae development had stopped in two of them. The side effects of oral *N*-acetylcysteine are mild, such as nausea, vomiting and diarrhea; none of which were observed in our patients.

In conclusion, oral *N*-acetylcysteine was effective in two of our three cases. This may suggest that *N*-acetylcysteine has a therapeutic merit in some pseudoporphyria patients with chronic renal failure.

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