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【 CASE REPORT 】

Hair Loss in a Hemodialysis Patient after Repetitive Use of the Antipruritic Drug Nalfurafine: Implications of Impaired Angiogenesis for Hair Loss

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Abstract:
A 47-year-old man who presented with scalp hair loss was transferred to our dialysis facility 3 months after hemodialysis initiation. He noticed systemic hair loss one month after the initiation of dialysis. Because the antipruritic drug nalfurafine was the only drug that had been newly added to his regular medication after he started hemodialysis, we stopped its prescription. His hair loss was completely ameliorated for the next five months. We speculated that κ-opioid receptor activation by nalfurafine caused blood capillary regression around the hair follicles, leading to cessation of hair growth and subsequent hair fallout.

Key words: hemodialysis, hair loss, pruritus, nalfurafine, κ-opioid receptor agonist, capillary regression

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Introduction

Chronic kidney disease (CKD) is an incurable and progressive disease characterized by a constant decline in the kidney function (1). The number of patients with CKD is growing continuously because CKD risk factors, such as aging, diabetes, and hypertension, are becoming increasingly prevalent (1, 2). The number of patients with end-stage kidney disease (the most advanced form of CKD) is also increasing and exceeded 2.5 million globally in 2017, being projected to double to 5.4 million by 2030 (3). Hemodialysis is the most common therapy used to treat patients with end-stage kidney disease (4).

Uremia is a broad term used to describe the buildup of metabolic waste products called uremic substances, such as urea, creatinine, and uric acid, in the blood due to a diminished kidney function (5, 6). Owing to the retention of such metabolic waste products, patients with end-stage kidney disease typically experience a constellation of symptoms, including nausea, vomiting, appetite loss, fatigue, muscle cramps, mental status changes, and pruritus. Pruritus (itch) is defined as an unpleasant sensation that elicits a desire to scratch (7). CKD-associated pruritus, also known as uremic pruritus, is a common, distressing, and under-recognized condition that affects over 40% of patients undergoing hemodialysis therapy (8). According to an international survey in 17 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) to assess treatment of CKD-associated pruritus, 69% of medical directors underestimated the prevalence of CKD-associated pruritus in their unit (9). Furthermore, 17% of hemodialysis patients do not report itching to any healthcare provider (9). In patients undergoing maintenance hemodialysis therapy, moderate to severe CKD-associated pruritus lowers patients' quality of life mainly via sleep disturbance and reduces their survival rate (8, 10, 11). However, there has been no effective treatment for severe CKD-associated pruritus for a long time. Therefore, effective therapeutic approaches for CKD-associated pruritus are needed.

Nalfurafine was the first medicine in the world to specifically treat chronic pruritus in patients undergoing hemodialysis (12, 13). This oral medicine suppressed CKD-associated pruritus signaling by activating the κ-opioid receptor in both the peripheral and central nervous systems (14). However, although nalfurafine was highly effec-

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tive in reducing CKD-associated pruritus, it demonstrated major side effects owing to its negative influence on the central nervous system, including insomnia, headache, vertigo, and nausea (12, 13).

We herein report a rare case of a hemodialysis patient who presented with scalp hair loss after repetitive nalfurafine use.

Case Report

A 47-year-old man who presented with hair loss was transferred to our dialysis facility as an outpatient. He had noticed hair loss on the scalp, trunk, and extremities one month after the initiation of hemodialysis. He had been receiving maintenance hemodialysis therapy (dialysis modality: hemodialysis using a cellulose triacetate dialyzer, three times per week, four hours per session) for three months since the development of end-stage kidney disease due to diabetic and hypertensive kidney diseases.

His height and weight were 165 cm and 72.0 kg, respectively, and his body mass index was 26.4. He had been working in the general administration field for 20 years. In terms of activities of daily living, the patient was able to walk, eat, and use the toilet independently. Although he had smoked 10-20 cigarettes per day for 25 years, he quit smoking after starting hemodialysis therapy. He did not drink at all and had no history of allergic reactions to the medication. He had a medical history of hypertension, type 2 diabetes, hypercholesterolemia, and reflux esophagitis. To control his blood pressure, we prescribed multiple antihypertensive agents including amlodipine (10 mg daily, calcium channel blocker), irbesartan (100 mg daily, angiotensin II receptor blocker), carvedilol (10 mg daily, β-receptor blocker), and furosemide (80 mg daily, loop diuretic agent). Other medications included linagliptin (5 mg daily, a dipeptidyl peptidase-4 inhibitor) for diabetes, atorvastatin (5 mg daily, a 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitor) for hypercholesterolemia, and esomeprazole (20 mg daily, a proton-pump inhibitor) for reflux esophagitis. In addition, he was taking fexofenadine (60 mg daily, histamine receptor antagonist) and nalfurafine (2.5 μg daily) for cutaneous pruritus, although he experienced very mild itching. He was injected with insulin glargine (2-4 units daily, long-acting insulin analog) to control blood glucose levels. His glycoalbumin levels were between 16% and 19%, indicating that blood glucose levels were well controlled.

He developed pruritus three months before the initiation of hemodialysis therapy (Fig. 1A). Because the severity of pruritus gradually and persistently increased, the patient constantly scratched his trunk and extremities, causing bleeding from multiple skin wounds. He reported that pruritus mildly affected his face and scalp. After visiting a dermatologist, he started regular use of a moisturizer and a topical corticosteroid, diflorasone diacetate, which showed a marginal effect on his pruritus. One month before the initiation of hemodialysis therapy, he developed a moderate-grade fever (38-40°C) (Fig. 1A). Concurrently, the symptoms of appetite loss and general fatigue were enhanced.

Table shows his laboratory measurements two weeks before the first hemodialysis session. The patient showed leukocytosis and mild anemia. His serum albumin level was low (2.9 g/dL) due to appetite loss. He showed high levels of blood urea nitrogen (110.4 mg/dL), serum creatinine (12.71 mg/dL), and serum phosphorus (9.3 mg/dL) and a low level of corrected serum calcium (6.3 mg/dL). As the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were not elevated, his pruritus was deemed not to have been derived from chronic cholestatic liver diseases.

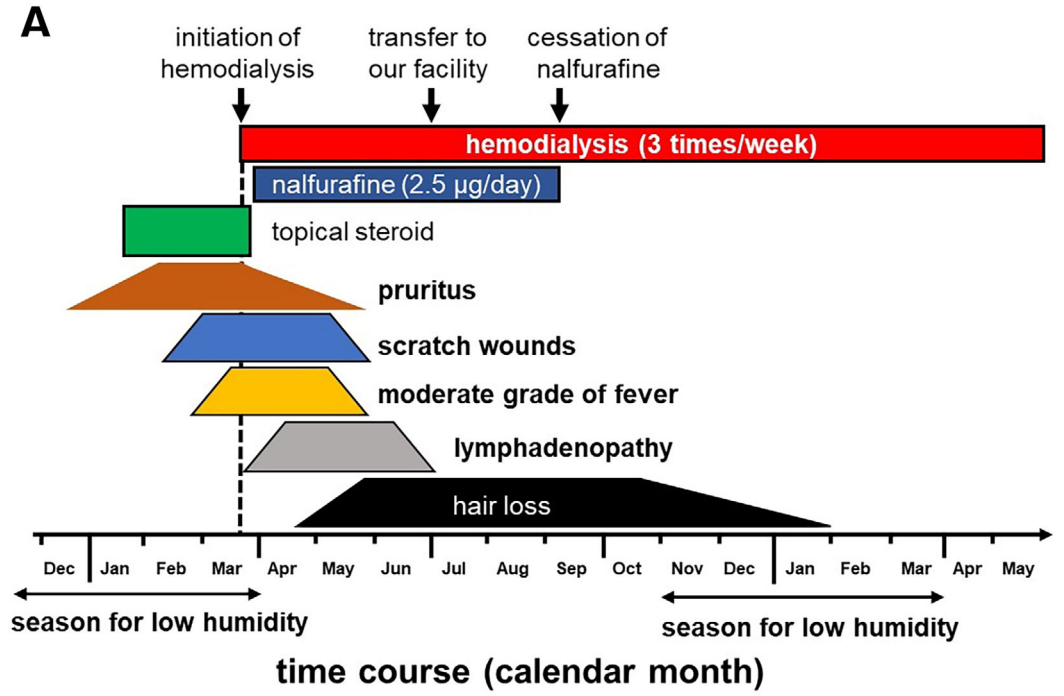
While the severity of pruritus was gradually alleviated after hemodialysis therapy was initiated, the patient still intensely scratched his whole body due to itching, resulting in bleeding from multiple skin wounds in the trunk and extremities. Therefore, to treat pruritus, he was prescribed nalfurafine (2.5 μg daily) 10 days after the initiation of hemodialysis therapy (Fig. 1A).

However, the patient started to demonstrate systemic lymphadenopathy in addition to a moderate-grade fever. He further reported that hair loss had started on his scalp, trunk, and extremities one month after dialysis initiation. His hair on the scalp easily came off even when he finger combed his hair. At the onset of hair loss, laboratory measurements revealed leukocytosis, mild anemia with iron deficiency, hypoalbuminemia (3.0 g/dL), and hypozincemia (54 μg/dL). Blood tests for his thyroid demonstrated a mild reduction in thyroid-stimulating hormone (TSH) and free triiodothyronine (F-T3), indicating low T3 syndrome (euthyroid sick syndrome) but not hypothyroidism (Table). These findings suggested that he was exhausted and malnourished due to chronic inflammation from the skin wounds.

Because the moderate-grade fever (38-40°C) and systemic lymphadenopathy persisted, he underwent multiple biopsies of the skin and lymph nodes 1 month after dialysis initiation, which did not show any malignancy. Skin biopsies revealed increased epidermal thickness and mild leukocyte infiltration (Fig. 1B, C). These findings indicated chronic eczema. Although multiple skin tissue samples were collected from his thighs and abdomen, they did not contain hair follicles, an organ responsible for hair growth. Based on the results of multiple biopsies, the patient was diagnosed with dermatopathic lymphadenopathy. Repetitive scraping causes skin damage and inflammation, thereby inducing a fever and systemic lymphadenopathy. Continuous hemodialysis therapy improved his pruritus, scratch wounds, moderate-grade fever, and lymphadenopathy (Fig. 1A). Therefore, three months after the initiation of hemodialysis, the patient was transferred to our dialysis facility for maintenance hemodialysis.

Clinical course after transfer to our facility

While his pruritus, skin wounds, and moderate-grade fever diminished, we noticed hair loss on the whole scalp re-



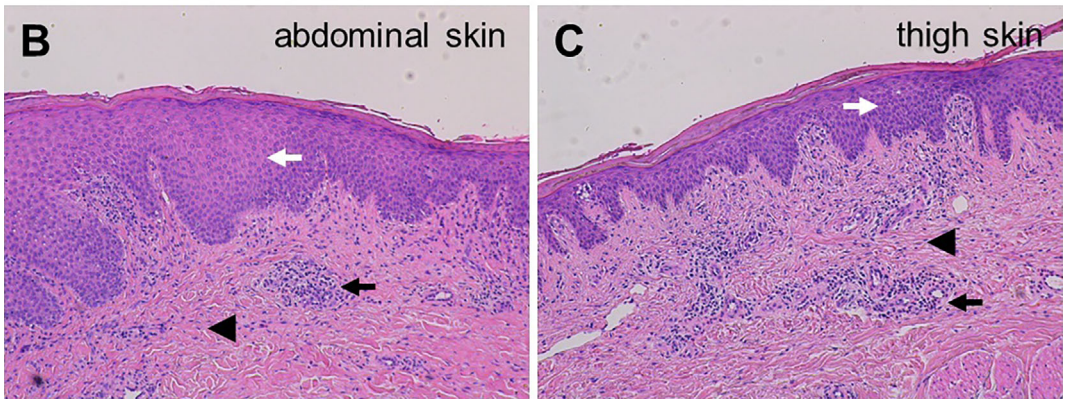


Figure 1. **Clinical features of the present case. (A) Treatment for pruritus and time course of symptoms in the present case. His pruritus (indicated by a brown trapezoid) worsened three months before the initiation of hemodialysis. Because topical steroid therapy (indicated by a green rectangle) was marginally effective, he intensely scratched his whole body, causing skin wounds. The scratch wounds (indicated by a blue trapezoid) triggered the development of a moderate-grade fever (38-40°C) (indicated by a yellow trapezoid) and systemic lymphadenopathy (indicated by a gray trapezoid). After the starting of hemodialysis, the symptoms of pruritus, scratch wounds, moderate-grade fever, and lymphadenopathy were gradually and persistently alleviated. One month after he started nalfurafine intake, he noticed systemic hair loss (indicated by a black trapezoid). Finally, his systemic hair loss was completely ameliorated five months after he stopped nalfurafine treatment. The five-month period from November to March is the typical season for dry skin with low humidity in our area. (B, C) Histology of skin biopsy samples from his abdomen and thighs. Biopsies were performed one month after the initiation of hemodialysis, when he still experienced moderate itching. Skin biopsy samples from his abdomen (B) and thighs (C) demonstrated increased epidermal thickness (indicated by white arrows), mild leukocyte infiltration in the dermis (indicated by black arrows), and mild deposition of collagen fibers (indicated by arrowheads). Those findings indicated chronic eczema. B, D: Hematoxylin and Eosin staining. Magnification ×100.**

gion, including the frontal, top, temporal, and occipital sides. His hair loss remained unchanged for two months after he was transferred to our dialysis center. Laboratory measurements no longer showed the excessive accumulation of uremic substances (Table). His nutritional status improved, as demonstrated by the nearly normal serum albumin value (3.9 g/dL). The anemia improved without iron deficiency. The zinc deficiency and hyperparathyroidism were

Table. Laboratory Data before Hemodialysis Initiation, at the Onset of Hair Loss, and at the Time of Nalfurafine Cessation.

Variable	Reference range	2 weeks before starting of hemodialysis	At the onset of hair loss	Just before cessation of nalfurafine
White blood cell count (per μL)	4,000-8,500	24,600	13,800	6,900
Hemoglobin (g/dL)	13.5-17.5	9.5	8.3	12.4
Platelet count (per μL)	120,000-360,000	310,000	261,000	308,000
Serum albumin (g/dL)	4.1-5.1	2.9	3.0	3.9
Alanine aminotransferase (ALT) (U/L)	8-40	15	21	11
Aspartate aminotransferase (AST) (U/L)	5-45	25	18	7
γ-glutamyl transpeptidase (γ-GTP) (U/L)	0-75	10	50	10
Alkaline phosphatase (ALP) (U/L)	38-113	101	94	72
Blood urea nitrogen (mg/dL)	8.0-23.0	110.4	43.7	45.5
Serum creatinine (mg/dL)	0.61-1.08	12.71	7.61	10.91
Uric acid (mg/dL)	3.8-7.0	15.6	8.6	7.1
Sodium (mEq/L)	136-147	135	140	137
Potassium (mEq/L)	3.5-5.0	4.4	4.1	4.3
Corrected serum calcium (mg/dL)	8.5-10.2	6.3	8.1	8.2
Serum phosphorus (mg/dL)	2.5-4.5	9.3	4.6	5.6
Serum iron (μg/dL)	60-200	-	18	101
Total iron binding capacity (TIBC) (μg/dL)	250-380	-	141	261
Serum ferritin (ng/mL)	13-277		183.2	89.5
C-reactive protein (CRP) (mg/dL)	0.00-0.30	0.18	1.63	0.02
Serum zinc (μg/dL)	80-130	-	54.0	67.0
Glycoalbumin (%)	11.8-16.0	-	19.0	16.8
Free triiodothyronine (F-T3) (pg/mL)	2.13-4.07	-	2.02	-
Free thyroxine (F-T4) (ng/dL)	0.95-1.74	-	0.86	-
Thyroid stimulating hormone (TSH) (μIU/mL)	0.34-3.88	-	0.26	-
Intact parathyroid hormone (PTH) (pg/mL)	18-88	320	-	279

Before dialysis initiation, our patient showed leukocytosis, mild anemia, and hypoalbuminemia, which may reflect chronic inflammation triggered by multiple scratch wounds throughout the body due to itching. Measurements also demonstrated a marked elevation in blood urea nitrogen, serum creatinine, uric acid, and serum phosphorus levels, indicating the accumulation of uremic substances. In contrast, no abnormalities were detected in the levels of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating that his pruritus was not derived from chronic cholestatic liver diseases. We detected mild elevation in parathyroid hormone levels in response to hypocalcemia and hyperphosphatemia. At the onset of hair loss (one month after dialysis initiation), the patient still showed leukocytosis, mild anemia with iron deficiency, and hypoalbuminemia. We also detected hypozincemia, which is found in most hemodialysis patients without hair loss. Measurements demonstrated slightly low levels of free triiodothyronine (F-T3) and thyroid-stimulating hormone (TSH), suggesting low T3 syndrome (euthyroid sick syndrome) in response to physical exhaustion. At the time of cessation of nalfurafine treatment (five months after dialysis initiation), the patient was no longer anemic and malnourished with no inflammation or scratch wounds. His iron deficiency had also improved. However, the patient still exhibited hair loss on the scalp, indicating that malnutrition and chronic inflammation were not the main causes of hair loss. Corrected serum calcium (mg/dL) was calculated using the following formula: serum calcium (mg/dL)+[4-serum albumin (g/dL)]. The reference range was based on laboratory data obtained at our dialysis facility and hospital.

alleviated. We did not observe any skin eruptions or other dermal changes on the scalp. We suspected drug-induced hair loss and found that nalfurafine was the only drug that had been newly started after the initiation of hemodialysis. Therefore, we discontinued nalfurafine. Despite no change in his hair loss over the next month, we finally recognized regrowth of his hair two months after cessation of nalfurafine (Fig. 2). His pruritus did not recur despite no further nalfurafine intake, and his scalp hair loss was completely ameliorated for the next three months (Fig. 1A, 2). Although we did not record images of his hair on the extremities and trunk before we stopped nalfurafine prescription, he described that hair regrew on the extremities and trunk at the same time his hair on the scalp did, suggesting that hair loss and hair regrowth systemically occurred in this patient.

Discussion

We encountered a rare case of a hemodialysis patient who developed scalp hair loss after repetitive use of nalfurafine for several months. Hair loss manifested one month after the first session of hemodialysis therapy. Nalfurafine was the only medication that he had started since the initiation of hemodialysis therapy. Furthermore, his hair regrew after the cessation of nalfurafine. When we first stopped the prescription of nalfurafine, he still experienced hair loss, even

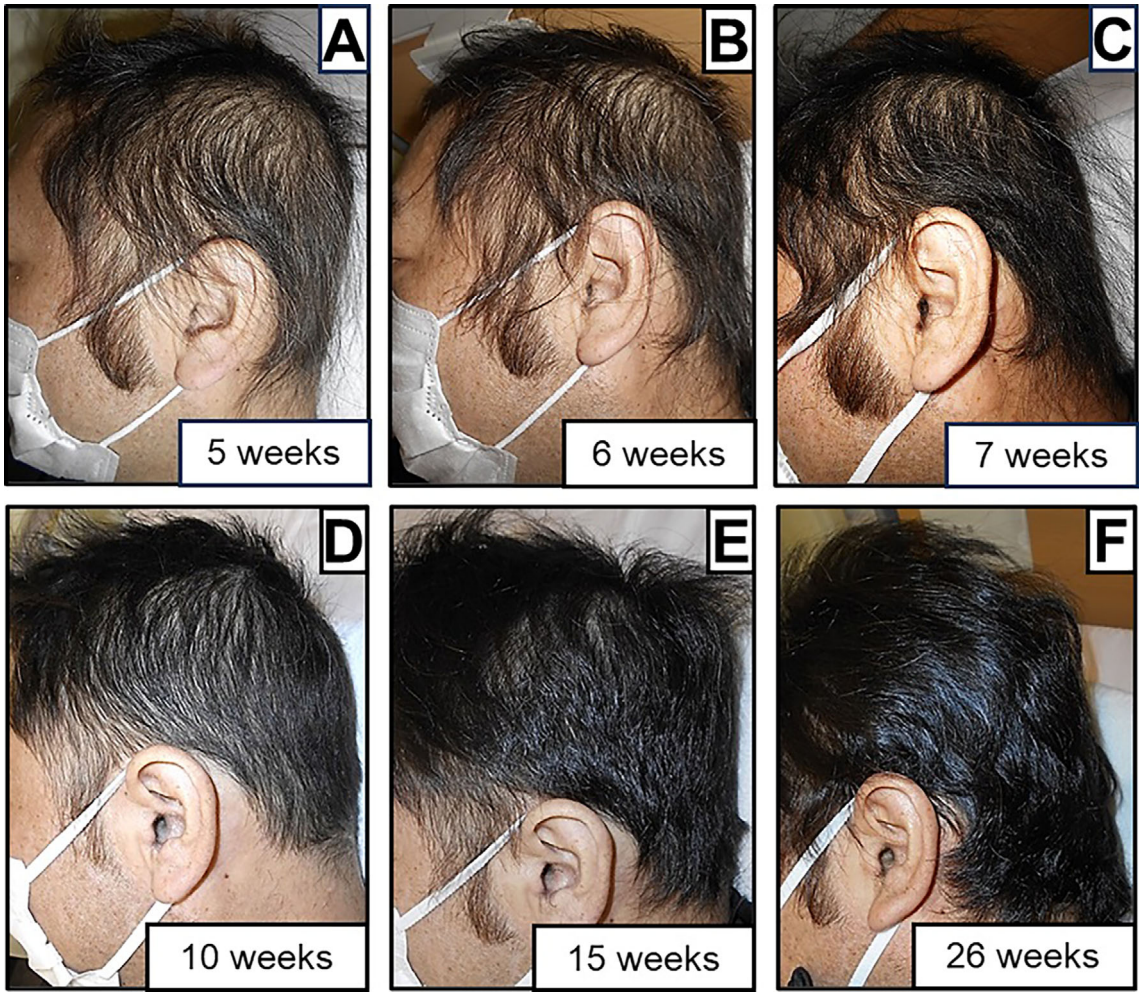


Figure 2. Clinical course of hair regrowth on the scalp after cessation of nalfurafine. Photo images demonstrate his hair regrowth on the left temporal side of his head. The number of weeks in each image indicate the time since cessation of nalfurafine prescription. (A, B) No remarkable change was observed in the degree of hair loss for the first six weeks after stopping treatment. Note that there were no abnormalities, such as skin eruption, on his scalp. (C) We detected hair regrowth seven weeks after he had stopped nalfurafine intake. (D, E) His hair persistently regrew without any exacerbation of pruritus. (F) His hair loss was completely ameliorated by 20 weeks and onward after cessation of nalfurafine.

though he was no longer anemic and malnourished without inflammation or scratch wounds. Other causes of hair loss, such as zinc deficiency and hyperparathyroidism, were also alleviated (15, 16). Taken together, we conclude that the repetitive use of nalfurafine caused hair loss in our patient.

To our knowledge, this is the first report to describe the causal association between nalfurafine use and systemic hair loss in a patient. However, in some cases, hair loss can manifest six months after the causative events. Thus, we cannot completely deny the possibility that malnutrition, chronic inflammation, and end-stage kidney disease directly induced hair loss independent of nalfurafine.

CKD-associated pruritus affects more than 40% of hemodialysis patients (8); however, the mechanisms underlying CKD-associated pruritus are not completely understood (17). Although one initial study identified histamine as a major cause of CKD-associated pruritus (18), subsequent studies revealed no relationship between plasma histamine levels and the extent of pruritus in patients undergoing hemodialysis (19). However, antihistamines are frequently used as the first-line treatment for pruritus (20). Ross et al. discovered using genetically engineered mice that inhibitory interneurons expressing basic helix-loop-helix b5 (Bhlhb5) in the dorsal horn of the spinal cord efficiently suppressed itch signaling by synthesizing several neuromodulators, including gamma-aminobutyric acid (GABA), glycine, and dynorphin (21, 22). Dynorphin is a potent endogenous ligand for the κ-opioid receptor (23, 24). In contrast, pruritic circuits are activated when the endogenous ligand β-endorphin binds to the μ-opioid receptor (25, 26). In other words, κ-opioid receptor agonists inhibit pruritic circuits, whereas μ-opioid receptor agonists enhance pruritic circuits (27). Since nalfurafine is similar in structure to dynorphin, nalfurafine efficiently binds to and activates the κ-opioid receptor located

in the peripheral and central nervous systems (14). Clinical trials have clearly shown that nalfurafine is an effective and safe compound for severe CKD-associated pruritus (12, 13), whereas μ-opioid receptor blocking by naltrexone did not relieve CKD-associated pruritus (28).

Three months before the initiation of hemodialysis, our patient developed pruritus, which was gradually and persistently relieved with hemodialysis therapy. Laboratory measurements showed high levels of blood urea nitrogen, serum creatinine, and serum phosphorus two weeks before the first hemodialysis session (Table). Phosphorus binds to calcium in the skin and causes pruritus (29). In addition, our patient's pruritic symptoms worsened in December, which is the typical season for dry skin with low humidity in the region (Fig. 1A). Thus, we finally concluded that pruritus was mainly triggered by dry skin and the accumulation of uremic substances.

Hair loss was not described in a post-marketing surveillance study of nalfurafine of more than 3,700 hemodialysis patients with intractable pruritus in Japan (30), indicating that hair loss is a very rare adverse reaction to nalfurafine. As major side effects were due to activation of κ-opioid receptor in the central nervous systems, hemodialysis patients with pruritus started to receive the peripheral selective agonist for κ-opioid receptor difelikefarin, which was also highly effective for CKD-associated pruritus (31, 32). Because its hydrophilic small peptide structure restricts passive diffusion across the blood-brain barrier, difelikefalin is expected to have a more favorable safety profile than nalfurafine (31, 32). These findings, together with experimental data, suggest that impaired κ-opioid receptor signaling in the peripheral nervous system (especially in primary sensory neurons) also contributes to CKD-associated pruritus (33).

To our knowledge, no reports have investigated the direct effects of κ-opioid receptor activation on hair growth. Therefore, the exact mechanisms underlying systemic hair loss in our case are still unknown. However, based on the findings of basic research, we propose that nalfurafine causes hair loss through impaired angiogenesis of the blood capillaries surrounding the hair follicle, an organ responsible for hair growth (Fig. 3A). First, the κ-opioid receptor is abundantly expressed in the vascular endothelial cells (34, 35). Second, κ-opioid receptor activation in vascularized lesions reduces the expression of vascular endothelial growth factor-A (VEGF-A) (36). Third, κ-opioid receptor activation inhibits the proliferation of capillary endothelial cells by decreasing the expression of VEGF receptor-2 (VEGFR2), a major receptor for VEGF-A (37). VEGF-A and VEGFR2 are the master regulators of angiogenesis that maintain the organ function (38, 39). Fourth, enhanced VEGF-A expression promotes vascularization around hair follicles, resulting in accelerated hair growth, whereas VEGF-A neutralization retards hair growth and reduces hair thickness (40). Fifth, in patients with cancer, alopecia was induced by inhibitors of VEGF-A signaling, such as bevacizumab (anti-VEGF-A antibody) (41) and ramucirumab (anti-VEGFR2 antibody) (42). Sixth, VEGF-A expression is markedly reduced in hair follicles of patients with alopecia areata or androgenic alopecia (43). Collectively, there was the possibility that nalfurafine induced systemic hair loss via downregulation of VEGF-A signaling and impaired angiogenesis around hair follicles.

At the bottom of the hair follicles, hair matrix cells surround the dermal papilla, which supplies oxygen and nutrients to the hair matrix cells via blood capillaries (Fig. 3A). The dermal papillae can signal hair matrix cells to proliferate and differentiate. Hair matrix cells act as germ cells that grow hair follicles and subsequently hair (44). As hair matrix cells continue to proliferate, hair follicles and hair cells grow longer. This process defines the hair growth cycle, which further categorizes the anagen, catagen, and telogen phases (45, 46). The anagen phase is the proliferation phase, which occurs when hair follicles grow new hair. For hair on the scalp, this growth phase lasts for two to six years. Approximately 85-90% of hair is in the anagen phase. The catagen phase is the regression phase, during which hair matrix cells stop proliferating, and hair follicles shrink. This phase lasts for only a few weeks, and only 1-2% of hair is in the catagen phase. Finally, the telogen phase ensues, referred to as the resting phase. Hair is detached from the hair follicles and no longer grows. This old and dead hair, called club hair, is shed passively by mechanical forces, allowing new hair growth to begin. The telogen phase typically lasts two to four months. Approximately 10-15% of hair is in the telogen phase.

We propose that nalfurafine causes capillary regression via inhibition of VEGF-A signaling and that regression of perifollicular and dermal papilla capillaries promotes the progression of the hair growth cycle from the anagen phase to the telogen phase (40). Regression of dermal papilla capillaries can induce apoptosis of hair matrix cells by lowering the supply of oxygen and nutrients from the dermal papilla to these cells, resulting in an increased number of hairs in the telogen phase, which is called atrophic telogen effluvium (47). Our patient's claims that his hair easily came off by combing suggests that most of his hair was in the telogen phase. He required a few months to regrow his hair, which may reflect the transition time for hair follicles to move from the telogen phase to the anagen phase.

Serum prolactin elevation is another possible mechanism that explains hair loss after nalfurafine treatment (48). However, a very high level of prolactin (400 ng/mL) is required to induce hair loss in organ-cultured human scalp hair follicles (48). This level of hyperprolactinemia is rarely detected in patients treated with nalfurafine (30). Furthermore, our patient did not experience erectile dysfunction or lactation, suggestive of hyperprolactinemia, although serum prolactin levels were not measured. Hyperprolactinemia was thus unlikely to be the cause of systemic hair loss in our case.

Finally, we speculated why our patient developed systemic hair loss, a rare side effect of nalfurafine, after its repetitive use. While 40% of nalfurafine is eliminated by the

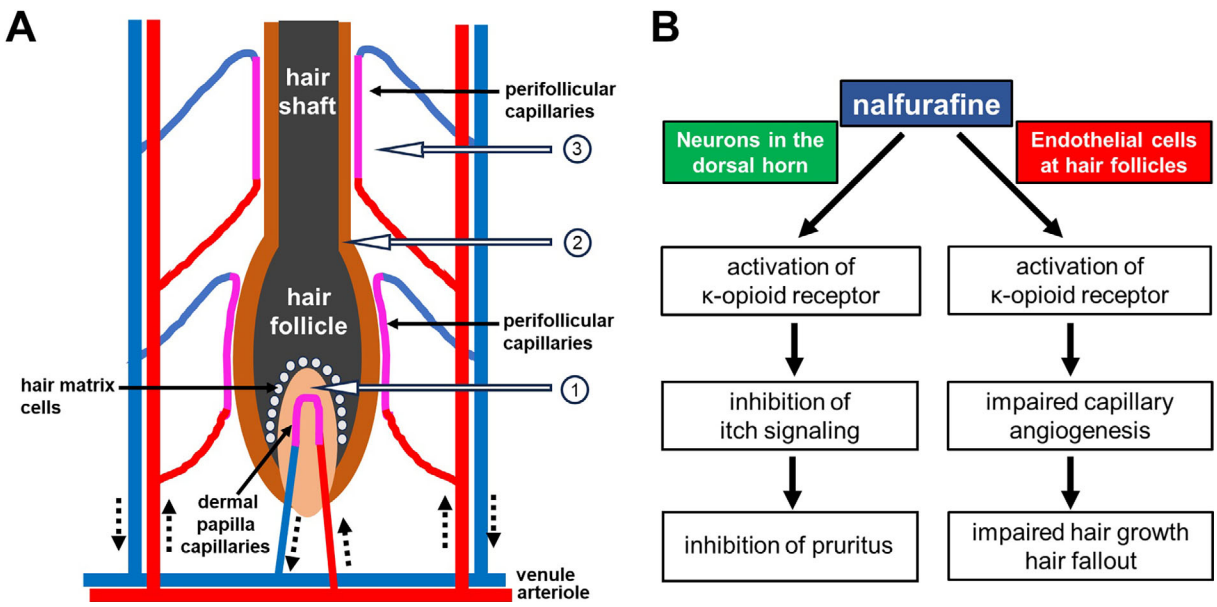


Figure 3. **Putative mechanisms of hair loss in the present case. (A) A schematic illustration showing the anatomy of blood capillaries around the hair follicle and in the dermal papilla. Arterial blood (indicated by red) moves through arterioles in the subcutaneous tissue and flows in the dermal papilla capillaries and the perifollicular capillaries (indicated by purple). After perfusing the tissue, venous blood (indicated by blue) flows in venules in the subcutaneous tissue. The dermal papilla capillaries nurture hair matrix cells (indicated by gray), whereas the perifollicular capillaries nurture the dermis and keratinocytes in the outer root sheath. Hair matrix cells generate the hair shaft. The outer root sheath anchors the hair root firmly to the scalp. Near the hair follicle, there are three spots that express vascular endothelial growth factor-A (VEGF-A): (1) dermal papilla, (2) keratinocytes in the outer root sheath, and (3) fibroblasts in the fibrous sheath (56). Those three spots are indicated by white arrows. Dotted arrows indicate the direction of blood flow. (B) Schematic illustration showing the putative mechanisms by which nalfurafine inhibits itch signaling and hair growth. Nalfurafine activates κ-opioid receptor on neurons in the dorsal horn of the spinal cord, which prevents those neurons from sending the itch signal to the brain. Separately, nalfurafine suppresses the itch signaling with κ-opioid receptor activation in the peripheral sensory neurons. Nalfurafine activates κ-opioid receptor on capillary endothelial cells in the dermal papilla and around the hair follicles and downregulates VEGF receptor-2 (VEGFR2) expression in those endothelial cells. Nalfurafine also decreases the expression of VEGF-A in the dermal papilla and the perifollicular areas. As VEGF-A signaling is the master regulator of angiogenesis, downregulation of VEGF-A and VEGFR2 causes capillary regression and resulting tissue hypoxia, leading to impaired function of hair matrix cells and keratinocytes in the outer root sheath. Those processes cause the cessation of hair growth and the detachment of hair from the scalp.**

kidney in urine, the remaining 60% is eliminated by the liver in bile and excreted in feces. Nalfurafine was removed from the body by dialysis in our patient. In the human liver, nalfurafine is metabolized to the decyclopropylmethylated form, mostly by three hepatic cytochrome P450 isoforms: CYP3A4, CYP2C8, and CYP2C19, where CYP3A4 is the major isoform (49). For reflux esophagitis, our patient regularly used esomeprazole (a proton pump inhibitor), which competitively inhibits CYP2C19 (50), indicating that regular use of esomeprazole could enhance the side effects of nalfurafine. Furthermore, inflamed or damaged skin tissues upregulate VEGF-A expression (51, 52). In our case, nalfurafine was continuously administered for a few months after pruritus was completely controlled, suggesting that the dermal expression of VEGF-A and VEGFR2 might be extremely low without skin inflammation. This could have contributed to hair loss in the present case.

To our knowledge, this is the first case of a hemodialysis patient in whom repetitive use of nalfurafine induced hair loss on the scalp and possibly on the whole body. We propose that hair loss was triggered by impaired capillary angiogenesis around the hair follicles due to κ-opioid receptor activation after nalfurafine administration (Fig. 3B). As capillary regression decreases the residual renal function and erythropoietin production in the kidney (53-55), the dose of nalfurafine should be minimized in patients with CKD-associated pruritus and end-stage kidney disease. Similar to nalufrafine, the peripheral selective κ-opioid receptor agonist difelikefalin has the potential to impair capillary angiogenesis through κ-opioid receptor activation. Therefore, adverse

effects should be carefully monitored.

We obtained written informed consent from the patient before preparation of our manuscript.

The authors state that they have no Conflict of Interest (COI).

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