AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

Pruritus in a Dialysis Patient

CLINICAL PRESENTATION

A 63-year-old man developed pruritus after 12 years of receiving dialysis through a left forearm arteriovenous fistula to treat end-stage renal disease of unknown cause. He experienced generalized chronic itching that was most intense on his upper back and worse during and after dialysis treatments and particularly at night. No medications or food affected the intensity of his pruritus.

The patient denied constitutional symptoms, symptoms of thyroid or liver disease, symptoms suggestive of neuropathic or psychogenic itch, pruritus in any other member of the household, herbal medication or alternative therapies, travel, or psychiatric history. He had a history of allergies (pollen and dust), hypertension, anemia, and hyperparathyroidism. His medications included trandolapril, beta erythropoietin, sevelamer hydrochloride, diphenhydramine, skin moisturizers, liquid powder with menthol, and gabapentin. Physical examination revealed no stigmata of other diseases. He did not have a rash or other skin lesions, except secondary excoriations on his upper back and mild skin scaling suggestive of xerosis.

Despite standard treatment, the intensity of the patient's pruritus worsened significantly, and he was admitted for further evaluation. Abnormal laboratory and imaging results are presented in Table 1.

Kidney failure and atopic diathesis were thought to be possible explanations for the elevated β_2-microglobulin and immunoglobulin E levels, eosinophilia, and anemia. The hematology department was consulted to rule out other potential causes for these findings. Peripheral-blood smear revealed only an elevated number of eosinophils. Computed tomography of the chest and abdomen produced unremarkable results. A blind skin biopsy was performed from the place of the most intense pruritus, and a specimen is shown in Fig 1.

Table 1. Laboratory and Imaging Results

Test	Results	Reference Range
SUN (mg/dL)	69.2	7.56-23.81
Kt/V	1.5	—
PTH (pg/mL)	1,070-1,200	10-65
Calcium (mg/dL)	10.46	8.50-10.1
Phosphorus (mg/dL)	6.63	2.42-4.74
Magnesium (mg/dL)	2.97	1.6-2.4
RBC count ($\times 10^6$/μL)	3.42	4.34-5.72
Hemoglobin (g/dL)	11.1	13.8-17.5
Hematocrit (L/L)	0.322	0.42-0.53
Eosinophils ($\times 10^9$/L)	2.02 (29.3%)	0.00-0.43 (0%-7%)
IgE (IU/mL)	2,720	≤100
β_2-Microglobulin (mg/L)	15.57	0.97-2.64
Ultrasound and scintigraphy	1 enlarged parathyroid gland	—

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; SUN in mg/dL to mmol/L, ×0.357.

Abbreviations: IgE, immunoglobulin E; PTH, parathyroid hormone; RBC, red blood cell; SUN, serum urea nitrogen.

- **What are the causes of pruritus in a dialysis patient?**
- **What is the appropriate evaluation for pruritus?**
- **What is the initial empirical treatment for dialysis-related pruritus?**
- **What does the skin biopsy show, and what is the diagnosis?**

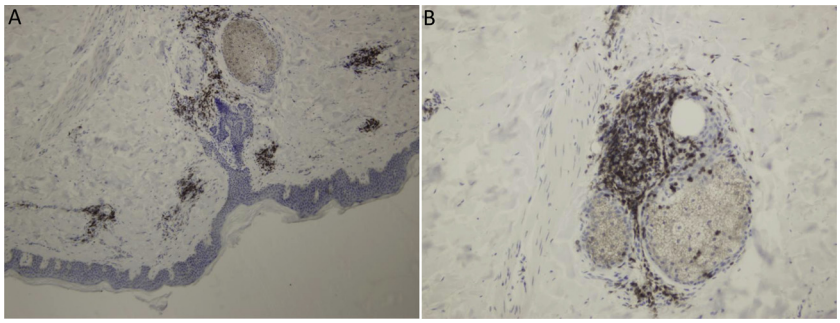

Figure 1. Skin biopsy specimen shows epidermis without overt changes. The skin adnexa (hair follicle and sebaceous gland) show periadnexal infiltration with T lymphocytes (predominantly CD3+), but without expected follicular mucinosis. Immunohistochemistry anti-CD3 stain (original magnification, [A] ×100); [B] ×200).

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

QUIZ PAGE AUGUST 2014 ANSWERS

DISCUSSION

What are the causes of pruritus in a dialysis patient?

Uremic or hemodialysis-related pruritus is a common and potentially disabling complication, and it often is difficult to treat. There are no pathognomonic dermatologic manifestations of hemodialysis-related pruritus, but most patients have xerosis with scaling and epidermal cracking. Repetitive scratching may result in secondary lesions, such as excoriations, lichen simplex, pruritus nodularis, keratotic papules, and follicular hyperkeratosis. Pruritus may be associated with a poor prognosis, making it a frustrating condition for both patients and physicians. Uremic pruritus may be the result of imbalance in the expression of μ and κ opioid receptors or systemic inflammation, with contributing factors such as xerosis and release of mast cell pruritogenes. The pathophysiology is poorly understood and a specific cause is still not identified. Potential causes are listed in Box 1.

Box 1. Potential Causes of Hemodialysis-Related Pruritus

- Inadequate dialysis
- Accumulation of poorly dialysed compounds
- Hyperparathyroidism
- Hyperphosphatemia
- Increased calcium-phosphate deposition in the skin
- Xerosis
- Elevated serum magnesium and aluminum concentrations
- Sideropenic anemia
- Hypersensitivity to products used in the dialysis procedure
- Hepatitis C virus infection
- Peripheral neuropathy
- Inflammation

What is the appropriate evaluation for pruritus?

Pruritus is a common symptom that occurs in a diverse range of cutaneous and extracutaneous diseases. Generalized pruritus has a broad differential diagnosis, including neurologic, psychogenic, systemic, and mixed disorders, sometimes associated with significant morbidity.

Many authors advocate that extensive laboratory investigation be reserved for patients with pruritus who have no evidence of skin disease on examination and do not respond to a short course of antipruritic therapy. There is controversy about initial and subsequent testing based on the patient's history and the level of suspicion for an underlying disorder (Box 2).[1,2]

Box 2. Evaluation of Pruritus

Initial tests:

- Complete blood cell count with differential
- Erythrocyte sedimentation rate
- SUN and Scr
- Serum bilirubin, transaminases, and alkaline phosphatase
- Fasting blood glucose and HbA_{1c}
- Thyroid function
- Parathyroid function (PTH, calcium, phosphorus levels)
- Serum iron and ferritin
- Chest x-ray

Additional tests:

- Stool examination for ova and parasites
- HIV antibody test
- Hepatitis B and C serologic tests
- Serum protein electrophoresis and immunoelectrophoresis
- ANA and other immunology testing
- Hypersensitivity testing (IgE, histamine, serotonin levels)
- Urine for 5-hydroxyindolacetic acid
- Other sonographic and radiographic imaging as needed

Abbreviations: ANA, antinuclear antibody; HbA_{1c}, hemoglobin A_{1c}; HIV, human immunodeficiency virus; IgE, immunoglobulin E; PTH parathyroid hormone; Scr, serum creatinine; SUN, serum urea nitrogen.

What is the initial empirical treatment for dialysis-related pruritus?

In the absence of another cause, one should assume that pruritus in dialysis patients is uremic

Box 3. Therapy for Hemodialysis-Related Pruritus

Initial therapy:

- Optimize dialysis
- Optimize treatment of hyperparathyroidism, hyperphosphatemia, and hypermagnesemia
- Use high water content emollients and/or topical analgesics, eg, pramoxine lotion, if symptoms persist
- Eliminate provocative factors (eg, wear appropriate clothing, exercise, relax, and avoid excessive bathing, hot food and drinks, stress and anxiety, or contact with dust and specific allergenes)

Therapy for resistant pruritus:

- Oral antihistamine
- Gabapentin (if resistant to 1- to 2-wk trial of antihistamine)
- UVB phototherapy
- Psychological approach and selective serotonin reuptake inhibitor antidepressant
- Kidney transplantation

Am J Kidney Dis. 2014;64(2):xviii-xxii

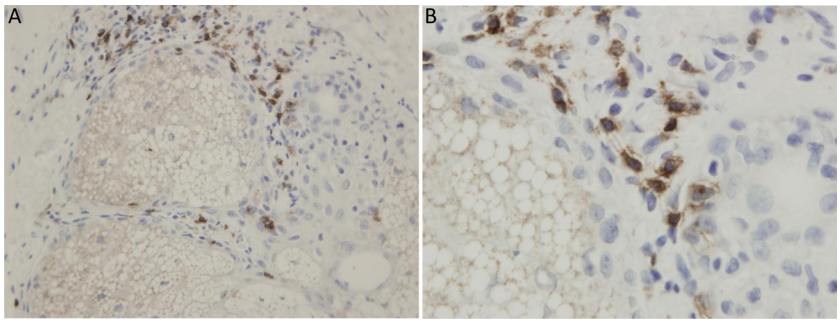

Figure 2. Skin biopsy specimen. Immunohistochemistry anti-CD8 stain; (A) original magnification, ×400: CD8 lymphocytes in epithelium of skin adnexa; (B) original magnification, ×1,000: CD8 lymphocytes with atypia in epithelium of skin adnexa.

pruritus. For those patients with resistant pruritus-continued symptoms despite adequate dialysis, optimization of metabolic parameters, and the use of topical emollients and analgesics for approximately 4 weeks, stepwise approach to treatment should be used as shown in Box 3.[1,3]

Although the intensity of pruritus may improve significantly after subtotal parathyroidectomy, pruritus is not always present in uremic patients with hyperparathyroidism, and there is no correlation between the severity of symptoms and parathyroid hormone, calcium, and phosphate levels.[1,3] In the absence of further studies, experimental therapies (eg, opioid receptor agonists and antagonists, omega-6 fatty acids, charcoal, 5-hydroxytryptamine receptors, and cromolyn sodium) should be considered only in patients with refractory symptoms. Topical tacrolimus should not be used.[3] Nonuremic causes of pruritus, especialy hematologic malignancies, cholestasis, and hypersensitivity reactions, should be considered in dialysis patients with pruritus resistant to conventional treatment.[3]

■ What does the skin biopsy show, and what is the diagnosis?

A biopsy specimen of skin that appears normal in a patient with generalized pruritus of unknown cause may provide valuable information.[1] In the case presented here, skin biopsy showed periadnexal infiltration by T lymphocytes with atypia, but without epidermotropism (Figs 1 and 2). This confirmed the diagnosis of mycosis fungoides (folliculotropic variant).

Mycosis fungoides is a rare, extranodal, indolent, mature T cell, non-Hodgkin lymphoma that develops primarily in the skin but ultimately can involve the lymph nodes, visceral organs, and blood. The folliculotropic variant has a markedly worse prognosis and is treated as extensive disease. Pruritus is one of the most common and debilitating symptoms of mycosis fungoides and typically is not present in the absence of cutaneous findings. Patients commonly present with persistent and/or slowly progressive skin lesions of varying size and shape that may affect any body surface. Establishing a definitive diagnosis usually takes months to decades and requires repeat skin biopsies.[4]

There are only a few case reports of pruritus preceding the onset of skin findings by several years[5,6] and only one documenting mycosis fungoides as a cause of pruritus in a hemodialysis patient, but in that case, the patient also had erythroderma and lymphadenopathy.[7] Our case would be the first description of "invisible" presentation of mycosis fungoides in a dialysis patient.

FINAL DIAGNOSIS

Mycosis fungoides (folliculotropic variant) in a dialysis patient, with rare presentation of persistent generalized pruritus with characteristics of uremic pruritus without skin lesions.

ACKNOWLEDGEMENTS

The authors thank Jasminka Mustendanagic, MD, MSc, and Mirzada Kurbasic, MD, MSCR, Professor at University of Louisville, for assistance in this case.

REFERENCES

1. Weisshaar E, Kucenic MJ, Fleischer AB Jr. Pruritus: a review. *Acta Derm Venereol.* 2003;(suppl 213):5-32.

2. Fazio SB, Yosipovitch G. Pruritus: etiology and patient evaluation. UpToDate. http://www.uptodate.com/contents/pruritus-etiology-and-patient-evaluation. Accessed September 12, 2013.

3. Tzeremas T, Kobrin SM. Uremic pruritus. UpToDate. http://www.uptodate.com/contents/uremic-pruritus. Accessed November 5, 2013.

4. Hoppe RT, Kim YH. Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides. UpToDate. http://www.uptodate.com/

contents/clinical-manifestations-pathologic-features-and-diagnosis-of-mycosis-fungoides. Accessed September 12, 2013.

5. Pujol RM, Gallardo F, Llistosella E, et al. Invisible mycosis fungoides: a diagnostic challenge. *J Am Acad Dermatol*. 2002;47(2)(suppl):S168-S171.

6. Hwong H, Nichols T, Duvic M. "Invisible" mycosis fungoides? *J Am Acad Dermatol*. 2001;45(2):318.

7. Miyoshi M, Ubara Y, Tagami T, et al. Mycosis fungoides in a hemodialysis patient with intractable pruritus. *Ther Apher Dial*. 2006;10(3):296-300.

CASE PROVIDED AND AUTHORED BY *Mirna Aleckovic-Halilovic, MD, PhD,[1] Enisa Mesic, MD, PhD,[1] Amila Jasarevic, MD,[1] and Alma Halilbasic, MD, MSc,[2] [1]Department of Nephrology, Dialysis, and Kidney Transplantation, Clinic for Internal Diseases, and [2]Clinic for Oncology, Haematology, and Radiotherapy, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina.*

Address correspondence to Enisa Mesic, MD, PhD, University Clinical Center Tuzla, Trnovac bb, 75000 Tuzla, Bosnia and Herzegovina. E mail: enisa.mesic@ukctuzla.ba

http://dx.doi.org/10.1053/j.ajkd.2014.02.030

SUPPORT: None.

FINANCIAL DISCLOSURE: The authors declare that they have no relevant financial interests.

QUIZ PAGE