The spectrum of nephrocutaneous diseases and associations

Genetic causes of nephrocutaneous disease

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Learning objectives
After completing this learning activity, participants should be able to recognize the important relationship between the skin and the kidney inclusive of genetic syndromes, recognize and differentiate the cutaneous manifestations of multiple kidney-related disorders, and vice versa, and describe the pathophysiology and genetic basis of how renal disorders may potentially manifest on the skin, and vice versa.

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There are a significant number of diseases and treatment considerations of considerable importance relating to the skin and renal systems. This emphasizes the need for dermatologists in practice or in clinical training to be aware of these associations. Part I of this 2-part continuing medical education article reviews the genetic syndromes with both renal and cutaneous involvement that are most important for the dermatologist to be able to identify, manage, and appropriately refer to nephrology colleagues. Part II reviews the inflammatory syndromes with relevant renal manifestations and therapeutic agents commonly used by dermatologists that have drug-induced effects on or require close consideration of renal function. In addition, we will likewise review therapeutic agents commonly used by nephrologists that have drug-induced effects on the skin that dermatologists are likely to encounter in clinical practice. In both parts of this continuing medical education article, we discuss diagnosis, management, and appropriate referral to our nephrology colleagues in the context of each nephrocutaneous association. There are a significant number of dermatoses associated with renal abnormalities and disease, emphasizing the need for dermatologists to be keenly aware of their presence in order to avoid overlooking important skin conditions with potentially devastating renal complications. This review discusses important nephrocutaneous disease associations with recommendations for the appropriate urgency of referral to nephrology colleagues for diagnosis, surveillance, and early management of potential renal sequelae. (J Am Acad Dermatol 2016;74:231-44.)

Key words: autoimmune; dermatology; genetic; genodermatoses; inflammatory; nephrocutaneous; nephrology.

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Table I. Renal findings in nephrocutaneous genodermatoses and recommendations on the timeliness of referral to a nephrologist if a patient has suspected or actual signs/symptoms of renal disease

Genodermatosis	Renal manifestations	Referral timeline
Neurofibromatosis type 1	Renal artery stenosis, Wilms tumor, and angiomyolipoma	Urgent
Tuberous sclerosis	Angiomyolipoma, renal cysts, and renal cell carcinoma	Urgent
Beckwith–Wiedemann syndrome	Wilms tumor, nephrolithiasis, renal cysts, hydronephrosis, and calyceal diverticula	As clinically indicated
von Hippel–Lindau syndrome	Renal cell carcinoma (clear cell variant) and renal cysts	Urgent
Birt-Hogg-Dubé syndrome	Renal cell carcinoma (oncocytoma and chromophobe variants) and renal cysts	As clinically indicated
Cowden syndrome	Renal cell carcinoma (papillary variant)	As clinically indicated
Hereditary leiomyomatosis and renal cell cancer	Renal cell carcinoma (papillary, tubulopapillary, and collecting duct variants)	Urgent
Fabry disease	Progressive renal failure	As clinically indicated
Nail–patella syndrome	Glomerulonephritis and end-stage renal disease	As clinically indicated
Turner syndrome	Horseshoe kidney, urinary collecting system anomalies, and decreased renal blood flow	As clinically indicated

INTRODUCTION

There are currently no comprehensive, up to date publications in the dermatologic literature relating to the wide spectrum of associations between cutaneous dermatoses and renal pathology. This 2-part review discusses important nephrocutaneous disease associations with specific recommendations for the diagnosis, management, and appropriate referral to nephrology specialists.

Part I of this two-part review focuses on the genetic relationships of nephrocutaneous diseases, and part II addresses inflammatory and medication-related nephrocutaneous associations.

GENETIC CAUSES OF NEPHROCUTANEOUS DISEASE

Table I is a summary of renal findings in the nephrocutaneous-associated genodermatoses with recommendations regarding when to refer to a nephrologist if one suspects a relationship between the skin and kidneys or if a patient exhibits signs or symptoms of renal pathology. In Table II, we include the known genetic mutations with gene locus as well as a summary of the cutaneous manifestations of these nephrocutaneous genodermatoses.

NEUROFIBROMATOSIS TYPE 1

Key points

- **Patients with neurofibromatosis type 1 have ocular, skeletal, neurologic, cardiovascular, neoplastic, and renal involvement in addition to their skin changes, necessitating multispecialty care coordination**
- **Dermatologists must be fully aware of the diagnostic skin criteria to ensure early coordination and appropriate renal evaluation**

Etiology

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen disease, is an autosomal dominant or spontaneous (30-50%) disorder with an incidence of 1 in 3000 live births. This condition is caused by a deletion mutation in the *NF-1* gene located on chromosome 17, which leads to truncation of the neurofibromin protein.[1-3] The neurofibromin protein is a GTPase-activating protein (GAP)–related protein and plays a crucial role in the negative regulation of the Ras–mitogen-activated protein kinase (MAPK) pathway, which promotes cell survival and proliferation. Ras activity requires GTP, and neurofibromin (in conjunction with other GAPs) accelerates the hydrolysis of GTP to GDP, depriving the Ras proliferation signal of the GTP required to propagate it.[4] In summary, neurofibromin functions as a tumor suppressor protein. The genetic pathway implicated in the pathogenesis of NF-1 is shown in Fig 1.

Cutaneous manifestations

Cutaneous findings in patients with NF-1 are almost universal and consist of café-au-lait macules, inguinal or axillary vault freckling, and cutaneous neurofibromas (Fig 2).[1,5-7] Plexiform neurofibromas may infiltrate deeply and diffusely and occur in approximately 25% of patients with NF-1. Malignant transformation of plexiform neurofibromas into malignant peripheral nerve sheath tumors occurs in 3% to 15% of patients with NF-1.[8] Other cutaneous findings in patients with NF-1 include glomus tumors and juvenile xanthogranulomas.

Other manifestations

Ocular complications, such as Lisch nodules (iris hamartomas), hypertelorism, and glaucoma