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Exceptional Case

Enigmatic pruritus in a kidney transplant patient

John E. Yates[1], Anthony J. Bleyer[2], Gil Yosipovitch[3], Omar P. Sangueza[4] and Mariana Murea[2]

[1]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA, [2] Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA, [3]Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, NC, USA and [4]Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC, USA

Correspondence and offprint requests to: Mariana Murea; E-mail: mmurea@wakehealth.edu

Abstract

Pruritus is a common problem following a kidney transplant and is usually attributable to new medications related to transplantation. We present an unusual case of pruritus that began several months after kidney transplantation. After changing several immunosuppressive medications, numerous clinical visits and consideration by the patient of stopping immunosuppression, scabies was diagnosed as the cause. Treatment with oral ivermectin and topical permethrin resulted in complete resolution of symptoms within 1 week. Transplant physicians should consider common causes of pruritus unrelated to transplantation; diagnostic skin lesions of scabies may be absent.

Keywords: pruritus; renal transplant; scabies

Introduction

Pruritus is the most frequent and distressing condition in dermatology, with an estimated prevalence in the general population of between 8.4 and 16.8% [1]. Pruritus is a widespread problem in patients with kidney disease, present in at least 25% of patients with chronic kidney disease, and up to 80% of patients with end-stage renal disease [2]. Prevalence of pruritus in patients following a kidney transplant has not been assessed in epidemiological studies. This case report presents a seemingly ordinary case of pruritus in a patient several months after kidney transplantation that progressed to severe pruritus. Improper diagnosis resulted in potentially harmful changes in the immunosuppressive regimen prior to quick resolution with appropriate diagnosis and therapy.

Case report

The patient is a 54-year-old Caucasian male with a history of chronic kidney disease secondary to focal segmental glomerulosclerosis (FSGS) who underwent uncomplicated, deceased donor kidney transplantation. Medications begun after transplantation included tacrolimus, mycophenolate mofetil, fluconazole, trimethoprim–sulfamethoxazole and valganciclovir. He had an uneventful post-transplant course that was characterized by good compliance and stable kidney function, with serum creatinine values ranging from 106.08 to 123.76 μmol/L (1.2–1.4 mg/dL) (normal: 53–106 μmol/L; 0.6–1.2 mg/dL).

Nine months after transplantation, the patient began to experience mild generalized pruritus with no rash. As the pruritus was mild and felt to be due to one of his medications, trimethoprim–sulfamethoxazole was changed to dapsone and the patient was prescribed an antihistamine for symptomatic relief. During his next clinic visit 1 month later, the patient was still symptomatic, and dapsone was discontinued. Full-body physical examination did not uncover skin lesions or discoloration, other than few self-inflicted linear excoriations secondary to pruritus. Direct anamnesis did not elicit any particular diurnal or nocturnal difference in the severity of pruritus. There were no provoking or alleviating factors such as heat, cold, contact with water or exercise. In the review of systems, he denied fevers, chills, nocturnal sweats, anorexia and weight loss. Blood tests, including a complete blood count with differential, hepatic function panel and thyroid stimulating hormone, were all within normal limits, and human immunodeficiency virus testing was negative.

Two months after the pruritus began, allograft biopsy was performed for decline in allograft function, and pathology revealed polyomavirus nephropathy; the immunosuppressive medications were decreased accordingly. Two weeks later, the serum creatinine rose to 212.16 μmol/L (2.4 mg/dL), and the patient underwent a repeat allograft biopsy revealing acute cellular rejection in the presence of persistent polyomavirus nephropathy. In light of these findings, he was admitted to hospital and treated with intravenous immunoglobulin, thymoglobulin and pulse steroids followed by a prednisone taper. His antimicrobial prophylactic medications were continued. It was anticipated that a higher dose of prednisone might ease the pruritus; however, it instead persisted

throughout the treatment. Three months after his initial complaint, his pruritus had become so uncontrollable that it was interrupting his sleep on a nightly basis, and working had become very difficult. Antimicrobial therapy was once again discontinued.

Thirteen weeks after commencement of pruritus, the patient was evaluated by dermatology. Physical examination revealed worsening diffuse linear excoriations induced by scratching without any other skin lesions. It was surmised that the pruritus was due to his immunosuppressive medications, and tacrolimus was changed to cyclosporine with no subsequent improvement in his symptoms. At 4 months, he was seen by dermatology consultants once again. Physical examination revealed no primary lesions, and therefore biopsy was not performed. Triamcinolone cream was prescribed, and the patient followed up with dermatology the following month. Due to persistent pruritus, he underwent a punch biopsy of his left anterior chest which revealed nonspecific inflammatory changes. The patient was started on ultraviolet light therapy, which proved unsuccessful.

Ten months after initial presentation, the patient had not responded to any treatments and continued to have severe generalized pruritus, so much so that the patient was considering stopping his immunosuppressive medications and allowing kidney rejection. He was seen again in the dermatology clinic. Examination of the skin revealed significant linear excoriations throughout the integument. At this time, minor scaling in his interdigital web spaces was noted. A wet mount was prepared and demonstrated scybala, or mite feces. The patient was treated with 12 mg ivermectin once, with a repeated dose 2 weeks later. He was also prescribed topical permethrin to be applied one time and repeated in 1 week. The patient was seen in follow-up 2 weeks later. After nearly 10 months of disabling generalized pruritus, the patient had no pruritus, and his secondary skin lesions were completely resolved. Only after treatment did the patient relate that several friends of his had also had problems with pruritus and likely scabies.

Discussion

Scabies has plagued mankind for more than 2500 years. There are accounts suspicious for scabies from the Old Testament and also from Aristotle in the fourth century B.C. [3]. In 1687, the obligate human parasite was first documented by Bonomo and Cestoni [4], who examined the organism under the microscope and produced drawings based on their findings (Figure 1). In modern times, scabies is estimated to infest 300 million people at any given time, with a prevalence ranging from 3.8% among sheltered and 56.6% among hospitalized homeless persons. Scabies has remained a huge social problem in numerous poor communities in South America, Africa and Australia, where it is hyperendemic, found as the most common skin disease in Ethiopia and Nigeria, and with a prevalence as high as 50% among Aboriginal children in northern Australia [3]. Transmission of scabies is by direct skin-to-skin contact of at least 15 min to transfer the mites from one person to another; it can also occur from heavily contaminated clothing or linens. After fertilization, the female mite burrows into the epidermis, laying eggs along the way. The larvae hatch in 3–4 days, travel from the burrow to the surface of the skin, copulate and continue the cycle [5].

Pruritus is the most prominent and common clinical feature of scabies. Host type I and IV hypersensitivity reactions involving multiple cell lines underline the pathophysiology of the scabietic rash and pruritus [6]. The itch is characteristically described as intense, intractable and generalized pruritus that usually spares the scalp. It is worse at night and after a hot shower, but occasionally patients are asymptomatic. In the classical presentation, physical exam reveals small, nonspecific erythematous papules and pathognomonic burrows typically involving the webs of the fingers, the flexor regions of the wrists and elbows, the skin immediately adjacent to the nipples, the groin and the buttocks and the male genitals (Figure 2A). The burrows appear as thin reddish or brownish lines that can be as short as a few millimeters; but they may be absent, and excoriations can also hide burrows from the physician's view. The head is normally spared in adults, but can be affected in very young children.

Atypical forms of scabies have been reported. Nodular scabies presents with violaceous pruritic nodules, commonly located on the thighs, axilla, glans and scrotum; or generalized (Figure 2B). Bullous scabies can mimic bullous pemphigoid clinically and histologically, and bullous lesions are frequently superinfected with *Staphylococcus aureus* (Figure 2C). There are case reports of patients who initially presented with generalized urticaria

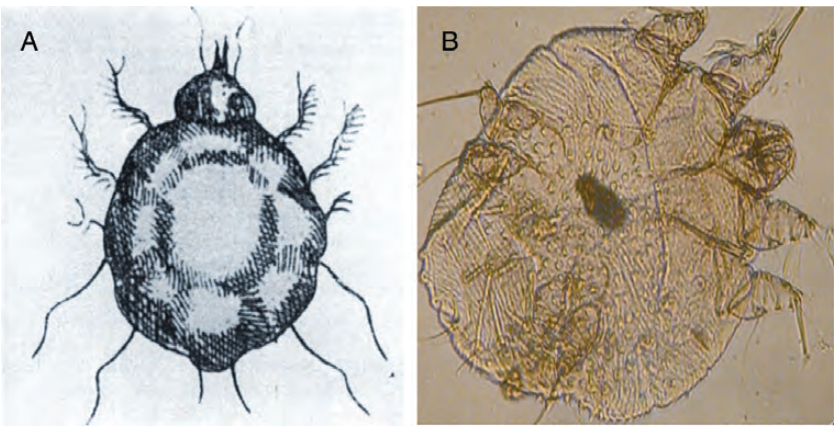

Fig. 1. *Sarcoptes scabiei* mite. (**A**) Drawing of the parasite as it appeared in Bonomo's 1687 letter [4]; (**B**) mites are not visible with the naked eye, but can be seen with a magnifying glass or microscope (average size 0.3 mm long).

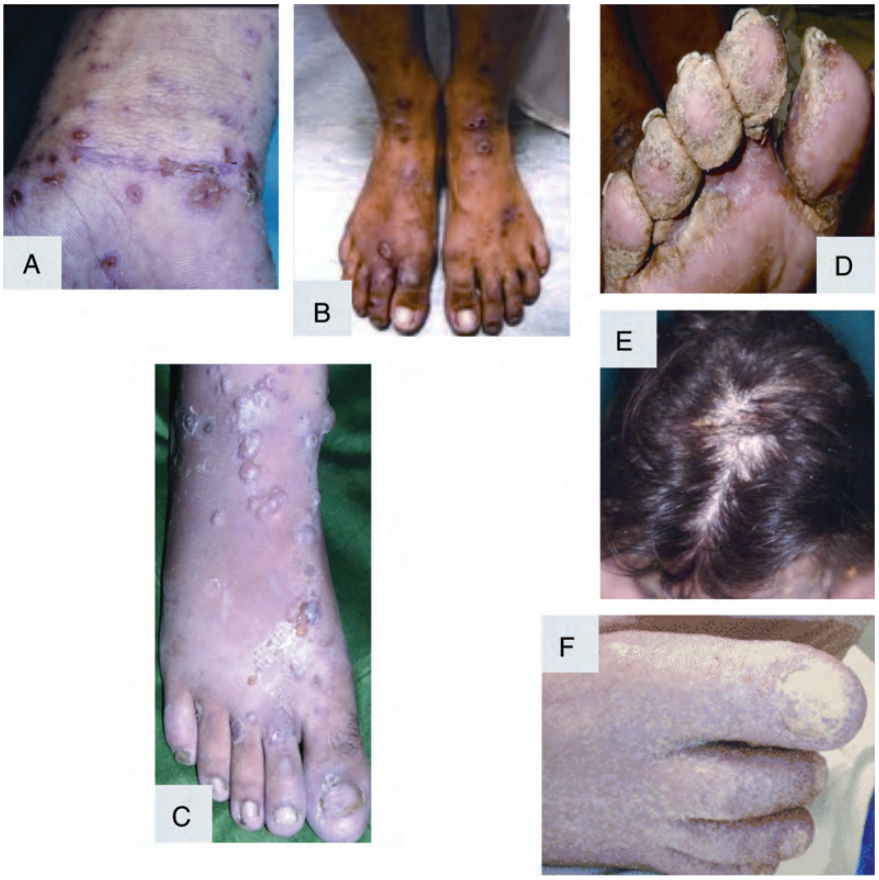

Fig. 2. Scabies skin manifestations. (**A**) Popular skin lesions; (**B**) nodular scabies; (**C**) crusted (Norwegian) scabies; (**D**) bullous scabies; (**E**) scaly scalp; (**F**) ungual scabies.

from scabies, but that is an exceedingly uncommon presentation. Crusted scabies, also known as Norwegian scabies, can occur in immunocompromised hosts, such as patients with AIDS, leprosy or lymphoma, or those who are undergoing treatments that reduce cellular immunity, such as organ transplant patients. This form of scabies initially presents with erythematous patches, and pruritus can be minimal or absent. These patches scale and subsequently become warty and malodorous. The scalp, hands and feet are often affected, but any area of the body may be involved (Figure 2D). If crusted scabies is left untreated, the disease may eventually involve the entire skin. Scabies of the scalp can occur in infants, children, elderly, immunosuppressed patients and patients with crusted scabies (Figure 2E). Subungual scabies can manifest as thickened, whitened nails, with or without nail plate deformity and subungual debris, involving one or several fingernails and/or toenails, as a singular manifestation of scabies or accompanying other skin lesions (Figure 2F). Severe hypersensitivity reactions can trigger monoclonal cell proliferations, generalized lymphadenopathy and eosinophilia; and immunohistochemistry may have features resembling leukocytoclastic vasculitis, mycosis fungoides or Langerhans cell histiocytosis [7].

The diagnosis of scabies is often made by taking a thorough clinical history and performing a careful physical examination. Severe itching that is worse at night, spares the head and is out of proportion to visible changes in the skin should raise suspicion for scabies. It should be ascertained whether or not any close contact, such as a household member, has had similar symptoms. The patient should be closely examined for any lesions such as the characteristic burrows. Diagnostic tests include skin scraping microscopy or dermoscopy, which can provide a more definitive diagnosis (Figure 3). Importantly, negative results with these tests do not exclude scabies. A study comparing microscopic evaluation of skin scrapings and *in vivo* dermoscopic mite identification revealed 90 and 91% sensitivity, respectively [8]. If clinical suspicion is mainly based on history alone, a therapeutic trial of antiscabietic medication may be tried.

Of note, serious complications can occur as a result of skin damage due to scabies mite infestations and bacterial superinfection. Specific scabies mite proteins act as complement inhibitors on all three complement pathways, inhibiting host innate immunity and fosters growth of streptococcal species [9]. Among other parasitic skin diseases (pediculosis, tungiasis, cutaneous larva migrans and myasis), scabies is the only parasitic skin infection for which a long-term sequel of skin colonization by group A streptococcus has been documented [10]. Occurrence of poststreptococcal glomerulonephritis (PSGN), acute rheumatic fever and systemic sepsis are well-known complications of scabies infestation. In remote indigenous communities of Australia, scabies underlies 50–70% of all cases of streptococcal skin infections and 40–50% of cases of scabiosis develop PSGN [11]. It has been documented for many years that high burden of

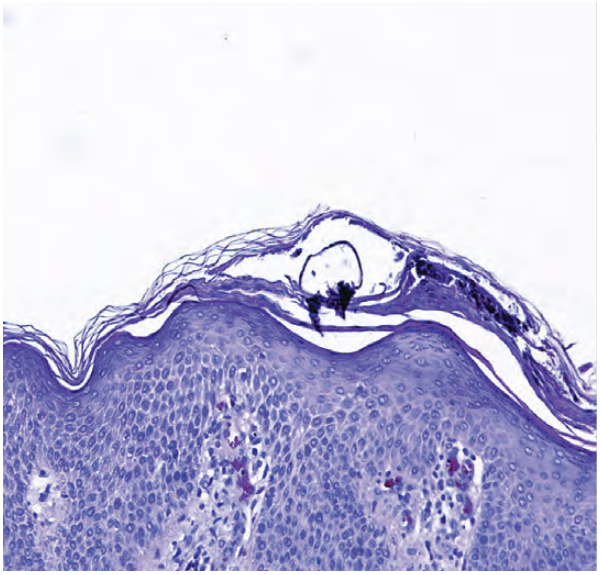

Fig. 3. Mite on H&E stain microscopy.

scabies infestation paralleled epidemics of PSGN, and large-scale interventions to eradicate scabies led to near obliteration of PSGN when successfully implemented [12, 13]. There has been a growing recognition that PSGN represents a strong risk factor for chronic renal failure. Previous history of PSGN and history of scabies *per se* associate with the presence of albuminuria and/or estimated glomerular filtration rate <60 mL/min later in life [14, 15]. It has been postulated that antibodies to mite antigens cross-react with basement membrane antigens, and therefore scabies could be intertwined with PSGN in a complex web of causation for chronic renal failure [16].

In this patient, the diagnosis was ultimately confirmed by his response to treatment since his presentation was atypical, and his physical examination was overall unremarkable.

The first-line therapy for scabies is topical permethrin or oral ivermectin [17]. Given the communicability of the disease, household members may require treatment. Antihistamines can also be tried to help further control severe pruritus. If symptoms worsen despite adequate treatment or reoccur, the patient should be asked about possible re-exposure.

Generalized pruritus is a fairly common finding in patients who have undergone kidney transplantation. Causes of generalized pruritus without skin lesions include a wide range of systemic disorders, psychiatric disorders, parasitic infestations and medications (Table 1) [18]. Two of the most common causes are uremic pruritus and medications. Uremic pruritus was unlikely in this case given the patient's good kidney function with a baseline serum creatinine value of 106.08–123.76 μmol/L (1.2–1.4 mg/dL). On the other hand, his medication profile did warrant further exploration, specifically tacrolimus. While calcineurin inhibitors are highly effective drugs for preventing transplant rejection, pruritus has been reported in up to 16% of patients treated with tacrolimus, and is more common with intravenous administration [19, 20].

This case demonstrates the shortcomings of the common diagnostic method used by physicians that is known as 'availability heuristics' [21]. Through experience, physicians develop techniques that allow them to diagnose disease efficiently. Rather than constructing a complete differential, physicians develop a diagnostic process based on their prior experiences. For transplant physicians, immunosuppressive medications are the most common cause of generalized pruritus, and these were considered primarily in the diagnosis. For nephrologists, uremic pruritus is extremely common and was considered in this case. Nephrologists and transplant physicians are highly specialized, and do not see scabies often, which is more commonly seen by the general practitioner. Furthermore, chronic steroids may obscure the diagnosis of scabies. In a retrospective study of hospitalized patients from long-term care facilities, chronic steroid use was identified as the risk factor among patients who had delayed diagnosis of scabies [22]. It is hard to believe that scabies could be life-threatening, but after 10 months of severe pruritus, the patient was considering withdrawal of immunosuppression and potential loss of allograft function, a move that would have considerably shortened his life expectancy.

Table 1. Causes of generalized pruritus without primary skin lesion

Category	Entity
Uremic pruritus	Chronic renal failure, end-stage renal disease, dialysis treatment
Hepatic pruritus	Chronic liver disease, cholestasis
Pruritus in hematologic diseases	Polycythemia vera, iron deficiency, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, lymphosarcoma, graft-versus-host disease, mycosis fungoides, mastocytosis, gastric carcinoma, carcinoid syndrome
Endocrine pruritus	Myxoedema, hyperthyroidism, hyperparathyroidism, diabetes mellitus
Neurogenic pruritus	Stroke, multiple sclerosis, brain tumor, brain abscess
Infectious illness	HIV, systemic parasitosis
Drug-induced pruritus	Most commonly with morphine, opioids, angiotensin-converting enzyme inhibitors, chloroquine and sulfonamides
Psychogenic pruritus	Psychosis, neurosis

Summary and Teaching Points

1. This case illustrates a unique presentation of disseminated scabies in a renal transplant patient whereby the diagnostic process was confounded for the following reasons: the patient had a history of kidney disease as a potential cause for generalized pruritus, and received medications known to cause pruritus.
2. The diffuse nature of his symptoms was unusual for scabies presentation, and no burrows were ever found on physical examination.
3. Largely through association with secondary bacterial infection caused by group A streptococci, the burden of the disease could be compounded by PSGN, rheumatic fever and sepsis.
4. Once the diagnosis of scabies is ascertained, the treatment is quick and successful.
5. Transplant physicians and nephrologists should remember to always consider scabies in their differential diagnosis when an immunocompromised patient presents with persistent pruritus.

Conflict of interest statement. None declared.

(See Editorial Comment by Tollitt *et al.* Of mites and men: scabies in patients with kidney disease. *Clin Kidney J* 2013; 6: 125–127)

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