

Cutaneous Mucormycosis Secondary to Acquired Reactive Perforating Collagenosis

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GOAL

To fully understand acquired reactive perforating collagenosis (ARPC)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the etiology of ARPC.
2. Explain the physical symptoms of ARPC.
3. Recommend treatment options for ARPC.

CME Test on page 110.

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Acquired reactive perforating collagenosis (ARPC) is a rare perforating disease of the skin. It is characterized by hyperkeratotic papules with transepidermal elimination of degenerated material including collagen and elastic fibers. The disease presents clinically as umbilicated papules with a central adherent keratotic plug. Mucormycosis infection, caused by the molds of the class Zygomycetes and order Mucorales, generally occurs as an opportunistic infection. It presents most frequently in patients with diabetes

mellitus, in patients with leukemia receiving chemotherapy, and in those on sustained immunosuppressive therapy.

We describe a patient with type 2 diabetes mellitus and end-stage renal disease requiring hemodialysis in whom extensive cutaneous mucormycosis with secondary spread to the brain, lumbar spine, and breast developed in the setting of ARPC. To our knowledge, this is the first case report of a patient with ARPC who developed extensive cutaneous mucormycosis.

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Acquired reactive perforating collagenosis (ARPC), first described in 1967 by Mehregan et al,¹ is a rare perforating disease of the skin characterized by hyperkeratotic papules with transepidermal elimination of degenerated material, including collagen and elastic fibers, that present clinically as umbilicated papules with a central adherent keratotic plug.¹⁻³ ARPC occurs more commonly in patients with diabetes mellitus and has been reported in 5% to 10% of patients undergoing hemodialysis.²

Mucormycosis, caused by the molds of the class Zygomycetes and order Mucorales, generally occurs as an opportunistic infection. It presents most frequently in patients with diabetes mellitus, in patients with leukemia receiving chemotherapy, and in those on sustained immunosuppressive therapy.⁴⁻⁷ Although most commonly found in the rhinocerebral form, mucormycosis also can present in a systemic or cutaneous form that frequently invades sites of impaired skin integrity.^{8,9}

We report a patient with ARPC who developed extensive cutaneous mucormycosis with secondary spread to the brain, lumbar spine, and breast.

Case Report

Over a 4-month period, a 61-year-old white woman with type 2 diabetes mellitus and end-stage renal disease requiring hemodialysis 3 times weekly developed multiple skin papules followed by night sweats and a 25-lb weight loss. The patient initially presented to the dermatology department at the Lahey Clinic Medical Center in Burlington, Massachusetts, complaining of severe pruritus and several small skin lesions that resembled warts (Figure 1). When the lesions enlarged, she was able to extract the core by the "root," yielding a gelatinous exudate. The histopathology of the lesion was consistent with ARPC (Figure 2).

Having achieved no relief from topical antipruritics over the subsequent month, the patient returned to the dermatology department. By that



Figure 1. Skin lesion on the lower left quadrant of the abdomen.

time, she had developed large necrotic plaques (approximately 8–12 cm in diameter) on her right lateral thigh (Figure 3) and smaller lesions on her anterolateral tibiofibular areas bilaterally. The infectious disease department was consulted, and the patient was admitted to the hospital for a wedge biopsy, diagnosis, and therapy.

On physical examination, the patient was a pale, elderly, afebrile, normotensive obese woman in no apparent distress. Her cardiopulmonary examination results were normal. The dialysis catheter site in her left anterior chest was not indurated or erythematous, though a left breast mass inferior to the dialysis port was noted. Examination of her skin revealed multiple ulcerated, umbilicated red-brown papules ranging from 4 to 8 mm, a few of which had a retained adherent keratotic plug. Most lesions had an area of central necrosis and were surrounded by an erythematous ring. Some exhibited a linear presentation (Köbner phenomenon). The two 8- to 12-cm necrotic ulcerations on the patient's right lateral thigh were acutely tender, were surrounded by a 3- to 4-mm erythematous border, and appeared to extend into the subcutaneous tissue.

Initial laboratory results included a leukocyte count of $7.6 \times 10^3 \mu\text{L}$ (75% neutrophils, 14% lymphocytes, 5% monocytes, 5% eosinophils), a serum urea nitrogen concentration of 58 mg/dL, and a creatinine level of 7.9 mg/dL. Transaminases, bilirubin, and alkaline phosphatase levels were within reference range. Blood cultures, both peripheral and from

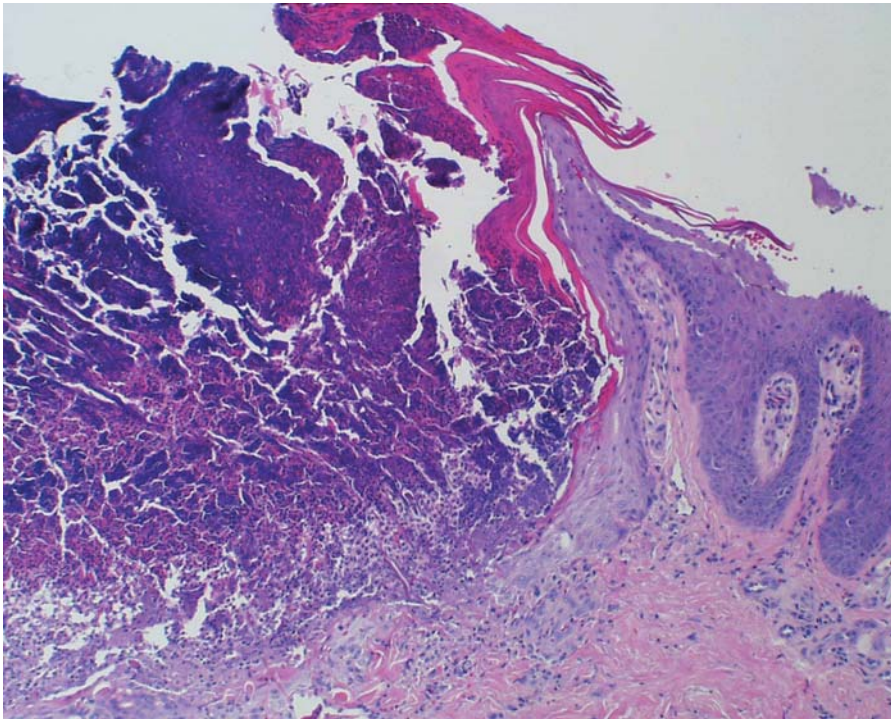


Figure 2. Results of initial biopsy specimen taken from the right upper thigh (H&E, original magnification $\times 40$).



Figure 3. Large necrotic plaques on the right lateral thigh.

the dialysis catheter port, grew coagulase-negative staphylococci. The dialysis catheter was removed and had more than 100 colonies of coagulase-negative staphylococci; fungal plate culture results were negative.

Pathologic examination of the biopsy of the gangrenous plaque on the right thigh revealed ischemic necrosis of the epidermis, dermis, and subcutis, with hyphal forms throughout the biopsy and within thrombosed vessel walls (Figure 4). Cultures grew mucormycosis, genus *Rhizopus*.

Plain films of the patient's femur and tibia demonstrated no bony destruction. Computed tomography of the chest and abdomen revealed a compression

fracture with a probable vertebral lesion and possible paraspinal abscess at the fourth lumbar vertebra. Magnetic resonance imaging of the central nervous system displayed focal areas of subacute hemorrhage that were consistent with a possible infectious process. Additional focal areas of abnormal enhancement were found within the right centrum semiovale and in the leptomeningeal space, suggestive of infection, infarct, or tumor. Results of the cerebral spinal fluid examination were unremarkable.

Treatment with lipophilic amphotericin B at 10 to 15 mg/kg per day and vancomycin were initiated; however, the patient's central nervous system disease and cutaneous lesions continued to

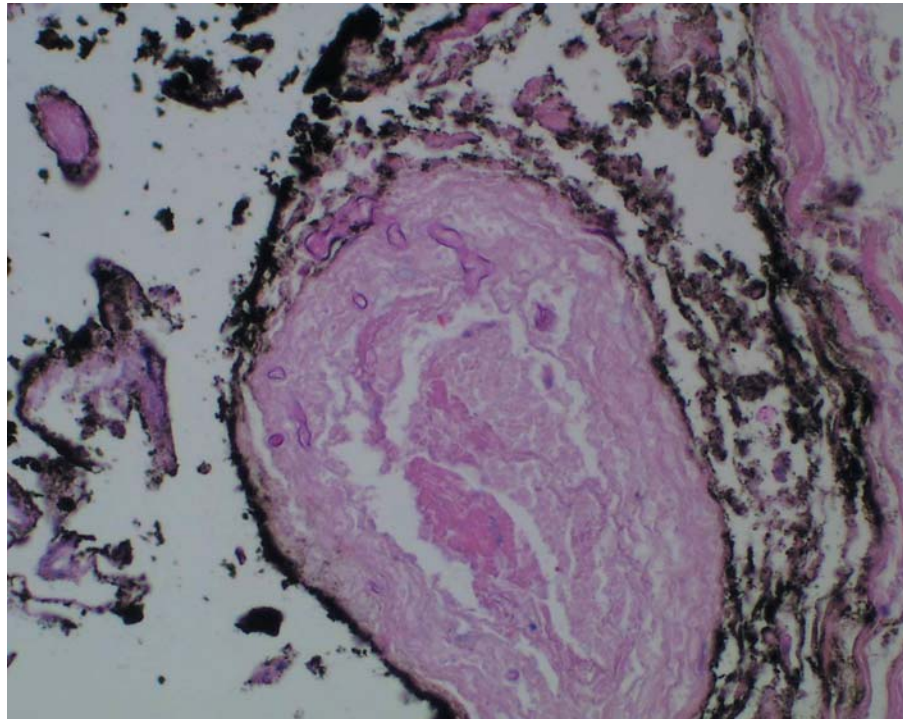


Figure 4. Results of wedge biopsy from the right thigh reveal a thrombosed and necrotic vessel in the deep dermis with intramural hyphal forms (H&E, original magnification $\times 400$).

progress. The small mass noted in her left breast on initial presentation rapidly increased to the size of a tennis ball. The infection in the thighs and tibiofibular areas were so extensive that surgical resection was not performed. The patient died of progressive disease after 3 weeks of hospitalization; permission for postmortem examination was not granted.

Comment

This patient presented with 2 unusual illnesses, ARPC and cutaneous mucormycosis, which may have had a cause-and-effect relationship. Both of these diseases are more likely to occur in patients with diabetes mellitus and end-stage renal disease. A comprehensive MEDLINE search of the literature published from 1969 to 2001 did not reveal an association of ARPC with mucormycosis.

Perforating collagenosis may present in 2 forms, an inherited autosomal-recessive form and a sporadic acquired form that may be associated with systemic diseases. As in our patient, most patients with ARPC also have diabetes or renal failure. In addition, the disease has been reported in 5% to 10% of all patients undergoing hemodialysis.^{2,10}

ARPC lesions have been speculated to develop from the chronic rubbing that occurs secondary to the xerotic pruritus of renal disease. The constant rubbing results in an epithelial hyperplasia, follicular hyperkeratosis, or prurigo-like lesions.² Diabetic

vasculopathy also has been projected as a predisposing factor for ARPC.³

Histologically, ARPC presents as altered dermal collagen bundles eliminated through the epidermis. Varying clinical and histologic findings are considered to be due to different stages of disease.

Cutaneous mucormycosis is a rare, acute, subacute, or chronic infection with only 116 cases listed in the English literature as of 2000. The mycelium of the Mucorales pathogen is composed of nonseptate coenocytic hyphae, which have a special affinity for blood vessels.¹¹ Cutaneous lesions initially present as erythematous papules or pustules but may rapidly evolve into necrotic ulcerations because the pathologic process of this angiophilic pathogen often involves early invasion of blood vessels, vascular occlusion, infarction, and ischemia.^{7,12} The broad nonseptate hyphae of *Mucor* are seen invading the vascular endothelium. *Mucor* fungi may cross fascial planes with little regard for tissue barriers by using proteases, lipases, and mycotoxins that may cause further infarction and tissue necrosis.

Although ubiquitous in the environment, particularly soil, *Mucor*, like other opportunistic saprophytes, almost never causes disease unless the patient also has underlying immunosuppression, neutropenia, or burns and there is direct cutaneous inoculation of the organism or spores at a site of trauma or impaired skin integrity.^{4,12} More than 85% of those

diagnosed with cutaneous mucormycosis have had trauma or a break to the skin integrity.⁹ Our patient's mucormycosis was distributed in the areas of her ARPC lesions, which could be reached and traumatized by the patient. Secondary hematogenous spread to her brain, lumbar spine, and breast most likely occurred. Another site of disseminated infection may have been the dialysis catheter, despite the negative culture results.

Cutaneous mucormycosis tends to present most frequently (31%) in the lower extremities. Of those patients who contract the disease, 20% also have diabetes, and 5% have renal failure. Mortality rates for patients diagnosed with cutaneous mucormycosis exceed 25% and are even higher if there is secondary dissemination.¹²

Cutaneous lesions may be the first sign of disseminated mucormycosis.¹³ Infection does not start through a cutaneous portal; rather, it usually arises from the inhalation of spores, followed by local infection and hematogenous spread.¹⁴ Evidence of cerebral infarction on a computed tomography scan can be due to vascular invasion by fungi with resultant thromboses.

Treatment strategies generally require intravenous amphotericin B therapy coupled with surgical excision and extensive debridement of the skin lesions.^{7,15} Correction of underlying predisposing medical conditions whenever possible is also helpful. Current oral azole antifungal agents and caspofungin generally are not useful in treating mucormycosis.⁵

The differential diagnoses of skin lesions resembling those of cutaneous mucormycosis include calciphylaxis, coagulopathic disease such as cryoglobulinemia, and the large vessel vasculitides such as polyarteritis, granulomatous vasculitides, and lymphoproliferative granulomatosis.

Conclusion

To our knowledge, cutaneous mucormycosis has not been previously reported in the setting of ARPC. Because ARPC is common in patients with diabetes and end-stage renal disease, physicians should be alerted to the possibility and potential complications of fungal, mycobacterial, or bacterial

opportunistic superinfection of these skin lesions and the necessity of appropriate diagnostic tests and early management and therapy.

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