

RESIDENT ROUNDS: PART III

Case Report: Fatal Cryptococcal Panniculitis in a Lung Transplant Recipient

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ABSTRACT

Cryptococcal panniculitis is a rare entity previously reported in only 13 solid organ transplant (SOT) recipients. Cutaneous cryptococcosis in SOT recipients warrants extensive systemic workup and treatment as if central nervous system (CNS) disease is present. It should be included in the differential diagnosis of panniculitis in the immunocompromised host, as early diagnosis and treatment are critical. We report a fatal case of cryptococcal panniculitis in a 44-year-old lung transplant recipient.

CASE REPORT

A 44-year-old man with cystic fibrosis, status post bilateral lung transplant 14 years prior, was admitted to the hospital for progressively worsening shortness of breath, headaches, and painful skin nodules on the legs and buttocks of 4 months duration. He had been on a longstanding immunosuppression regimen of tacrolimus, mycophenolate mofetil, and prednisone. Five months prior, his pulmonologist noted decreased pulmonary function tests, and a chest X-ray revealed a new right mid-lung mass. A computed tomography (CT) of the chest was recommended for further evaluation but he did not follow up.

During this time he developed painful skin nodules on his thighs and buttocks. An initial biopsy performed by an outside dermatologist was read as erythema nodosum. His shortness of breath worsened and he developed new headaches, prompting hospital admission. He did not have fever, chills, or night sweats. He denied sick contacts, recent travel, and exposure to pets or birds. He had lived his entire life in the Northeast region of the United States and was employed as a bookkeeper at a library.

On admission, his vital signs were normal. Tender red 1 cm to 5 cm subcutaneous nodules were scattered on both medial thighs and buttocks (Figure 1). A CT scan of the chest revealed a 3.8 cm x 2.0 cm cavitory mass in the superior segment of the right lower lobe. A skin biopsy showed numerous non-encapsulated yeast cells in the subcutaneous fat with a gelatinous-type histologic reaction (Figure 2). A culture of skin biopsy showed mucoid colonies of *Cryptococcus neoformans*

on 5% sheep blood agar (Figure 3). The initial “erythema nodosum” skin biopsy, from several weeks prior, was positive for multiple yeasts with surrounding halos using a gomori methenamine silver stain.

A lumbar puncture was performed and cerebrospinal fluid (CSF) was positive for cryptococcal antigen at 1:1024. The India ink stain of the CSF is shown in Figure 4. The patient was started on intravenous amphotericin B (lipid complex) 300 mg Q12 hours along with oral flucytosine 1 g Q12 hours. He was discharged 10 days after admission with a peripherally inserted central catheter to continue treatment, but was readmitted 1 week later with recalcitrant disease. Despite continued aggressive anti-fungal therapy (including the addition of voriconazole 230 mg Q12 hours), he died 8 months later from complications of disseminated disease.

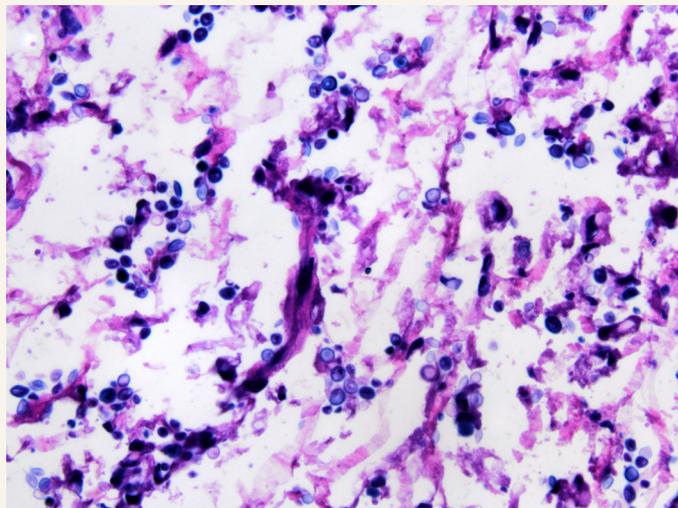
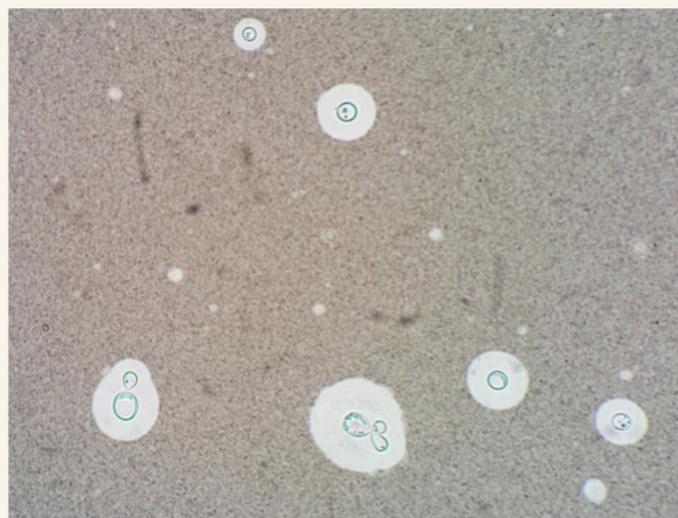
DISCUSSION

Cryptococcus neoformans is an opportunistic fungal infection with significant morbidity and mortality in the immunocompromised host. Solid organ transplant (SOT) recipients with disseminated disease account for 30% to 60% of non-HIV patients infected with *Cryptococcus*, and carry a mortality rate of 33% to 42%.^{1,2} The central nervous system (CNS) serves as the most frequent site of dissemination from the primary pulmonary disease, followed by the skin and soft tissue (10%-20%). Cutaneous cryptococcosis in SOT recipients almost always results from disseminated disease, and primary cutaneous cryptococcosis (PCC) should be a diagnosis of exclusion.³ Cellulitis is the most common cutaneous mani-

FIGURE 1. Tender red subcutaneous nodules on medial thigh.**FIGURE 3.** A culture of skin biopsy showing mucoid colonies of *Cryptococcus neoformans* on 5% sheep blood agar.

festation of disseminated cryptococcosis in SOT patients, with multiple other morphologies described in disseminated disease.⁴ Cryptococcal panniculitis is a rare entity reported in only 13 SOT recipients (12 renal, 1 heart), all males, with most presenting with painful lower extremity involvement; cryptococcal panniculitis has not been previously reported in a lung transplant patient (Table 1).⁵

The Infectious Diseases Society of America (ISDA) and the American Society of Transplantation recommend treatment of cutaneous cryptococcosis as if CNS disease is present.

FIGURE 2. Hematoxylin and eosin (H&E) staining of skin biopsy shows numerous non-encapsulated yeast cells in the subcutaneous fat with a gelatinous-type histologic reaction (100x magnification).**FIGURE 4.** An India ink stain of cerebrospinal fluid shows budding yeast cells surrounded by wide gelatinous "halo" capsules, characteristic of *Cryptococcus neoformans*.

Treatment consists of the following 3 stages:

1. *Induction:* liposomal amphotericin B and 5-flucytosine for 2 weeks;
2. *Consolidation:* high-dose fluconazole (400 mg/day to 800 mg/day) for 8 to 10 weeks;
3. *Maintenance:* low-dose fluconazole (200 mg/day) for 6 to 12 months.⁶

A lumbar puncture should be performed after induction to ensure eradication of CNS disease, prior to proceeding to

TABLE 1.

Cryptococcal Panniculitis in Solid Organ Transplant Recipients							
Case	Age/ Gender	Transplant	Interval Between Transplant and Infection (Years)	Cutaneous Presentation	Cerebrospinal Fluid Involvement	Pulmonary Involvement	Reference
1	48 M	Heart	11	Tender, subcutaneous plaques on medial thighs, right foot, and left flank	+	?	5
2	52 M	Kidney	5	Red plaque with central bullae on necrotic area of left leg stump	-	?	10
3	55 M	Kidney	8	Tender subcutaneous nodules on right forearm and "cellulitis" on leg	-	?	10
4	33 M	Kidney	13	Non-tender plaques on left thigh	-	+	11
5	54 M	Kidney	3	Left leg "cellulitis"	-	-	12
6	46 M	Kidney	6	Erythema, swelling, and tenderness from left thigh to ankle	?	?	13
7	45 M	Kidney	9	Tender, indurated plaques on right thigh, left arm, right arm, and left forearm	+	+	14
8	57 M	Kidney, Liver	31 from Kidney, 1/3 from Liver	Tender subcutaneous nodules and plaques on thighs and ankles	+	?	15
9	57 M	Kidney	5/6	Erythema, induration, and tenderness of right medial thigh	-	+	16
10	41 M	Kidney	8	Erythema, tenderness, and edema of left calf	+	+	17
11	57 M	Kidney	10	Erythema, swelling, and warmth of medial left calf	?	?	17
12	61 M	Kidney	11	Tender ulceronecrotic plaques on lower legs, 8 x 8 cm black eschar on lateral right lower leg	-	?	18
13	45 M	Kidney	1/3	Tender red nodules on thighs	-	+	4
14	44 M	Lung	14	Tender red nodules on thighs and buttocks	+	+	Present case

consolidation. If CNS disease is present, induction should be continued until CNS is sterile. Surgical excision of pulmonary or cutaneous cryptococcus remains a controversial treatment modality that is sometimes used in cases of anti-fungal inefficacy or severe anti-fungal side effects (ie, nephropathy from amphotericin).

Surgical removal of pulmonary or skin lesions is currently limited to case reports, with no published prospective studies. There have been several published cases of relapse-free survival in patients who had undergone surgical intervention along with anti-fungal therapy for PCC. However, there have been reports of detrimental effects of surgical intervention, as demonstrated in a case of PCC in a lung transplant patient for whom surgical debridement of the skin was suspected to

have caused dissemination with CNS involvement.⁷⁸ In the absence of unifying data, we propose that the surgical removal of cryptococcal lesions in the immunocompromised host should be reserved for diagnostic purposes, cases refractory to medical treatment, or solitary skin nodules amenable to excision and primary closure.^{4,9}

DISCLOSURES

None of the authors has declared any relevant conflicts of interest.

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