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Histoplasmosis and subcutaneous nodules in a kidney transplant recipient: erythema nodosum versus fungal panniculitis

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Abstract

Erythema nodosum (EN)-like lesions are a rare occurrence after solid organ transplantation. Differential diagnosis includes infective panniculitis, which can be a feature of progressive disseminated histoplasmosis (PDH), an uncommon but severe form affecting primarily immunocompromised hosts. We report on a fatal case of PDH, which presented as fungal panniculitis masquerading as EN in a renal allograft recipient 25 years after transplantation. We discuss the clinical, histopathological, and microbiological characteristics of this rare complication, with focus on its distinction from EN. This case emphasizes the central role of biopsy in transplant recipients presenting with cutaneous lesions, and the importance of clinicopathologic correlation and complementary microbiological investigations.

Keywords

histoplasmosis; progressive disseminated histoplasmosis; solid organ transplantation; renal transplant; kidney transplant; erythema nodosum; fungal panniculitis; infective panniculitis; granulomatous panniculitis

Erythema nodosum (EN) is the most common clinicopathologic variant of panniculitis, presenting clinically as painful pretibial erythematous nodules. It is considered an immune-driven process, triggered by numerous infectious and non-infectious processes (1). Its differential diagnosis encompasses potentially life-threatening diseases, such as cutaneous lymphoma, and other types of panniculitides, including infective panniculitis (2, 3). In the latter, microorganisms directly invade the subcutaneous tissue in the setting of localized or disseminated infection. *Histoplasma capsulatum*, a dimorphic fungus that is endemic along the Mississippi, Ohio, and St. Lawrence Rivers (4), has been incriminated in both EN and infective (fungal) panniculitis (5–8). While the former has been described in acute self-limited forms, the latter is seen in progressive disseminated histoplasmosis (PDH) (9–20), a form arising in immunocompromised patients, such as solid organ transplant recipients (SOTR), who fail to mount an appropriate cellular immune response. EN-like lesions are a rare occurrence in SOTR; however, establishing an etiologic diagnosis is critical—albeit very challenging at times—in order to assure appropriate therapy. Herein, we present a case

of fungal panniculitis, as the presenting finding of fatal PDH, masquerading as classical EN in a kidney transplant recipient, 25 years after transplantation.

Case report

A 53-year-old female kidney transplant recipient from Southeast Pennsylvania was transferred to our institution after, 2 weeks of care in another hospital with pneumonia. She had received 3 kidney transplants (the last 25 years before this presentation) because of end-stage renal disease secondary to post-streptococcal glomerulonephritis. Her immunosuppressive regimen consisted of prednisone (alternating 5 mg and 10 mg orally every other day) and azathioprine (25 mg orally daily).

Three months before her presentation, she developed painful palpable erythematous skin lesions on the anterior surface of her lower extremities. At the time, she was being evaluated for continuous ambulatory peritoneal dialysis because of chronic allograft failure and the lesions were initially thought to be a result of calciphylaxis. An interferon-gamma release assay (IGRA) for tuberculosis (TB) (Quantiferon-TB Gold InTube; Cellestis, Inc, Valencia, California, USA) performed as part of a pre-dialysis workup was positive; therefore, treatment with isoniazid was initiated for presumed latent TB infection (LTBI). The treatment was stopped prematurely after 1 month because of pruritus. At that time, an incisional skin biopsy was performed on a left thigh lesion and reported as consistent with EN. Special stains, including Grocott's methenamine silver (GMS), were unrevealing. EN was assumed to be associated with her recent LTBI diagnosis. She was treated with oral super-saturated potassium iodide and later on with systemic corticosteroids (intramuscular betamethasone). Despite receipt of EN-directed therapies, new skin lesions appeared.

She was eventually admitted to her hospital with a subacute history of fatigue, dyspnea, and dry cough, in addition to newly appearing skin lesions. She was febrile (39.4°C) and hypoxemic at presentation. A computed tomography scan of the thorax revealed bibasilar peribronchial thickening with patchy infiltrates. A bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy were performed. Microscopic examination of BAL fluid revealed yeast cells on GMS stain that were not compatible with *Pneumocystis jirovecii* and thought to be colonizing *Candida* species. Other stains and cultures were negative, including those for mycobacteria and cytomegalovirus. Transbronchial biopsy showed nonspecific chronic inflammation. A bone marrow biopsy was also performed and failed to identify any organisms on special stains. A punch skin biopsy from a lesion on the right thigh demonstrated panniculitis with numerous small budding yeasts. Her condition deteriorated despite broad-spectrum antimicrobial therapy (including caspofungin) and she required intubation and administration of vasopressors.

After 2 weeks of hospitalization, the decision was made to transfer the patient to our hospital. Upon admission in our intensive care unit, she was alert and appropriately responsive despite endotracheal intubation and intermittent vasopressor requirement. Erythematous tender plaques of 3–6 cm were noted on the extensor surface of upper and lower extremities. The abdomen was soft and non-tender. One febrile episode was observed at 38.4°C on day 2. Pertinent laboratory and microbiological data are presented in Table 1. A chest and abdomen computed tomography showed multifocal ground-glass opacities in the lungs, a hypodense lesion in the liver and heterogeneous enhancement of the spleen and transplanted kidney. Treatment was initially adjusted to piperacillin-tazobactam (2.25 g intravenously [IV] every 6 h) and azithromycin (500 mg IV daily). A serum *Aspergillus* galactomannan antigen (GMA) enzyme immunoassay (EIA) (Platelia™ *Aspergillus* EIA, Bio-Rad Laboratories Inc., Hercules, California USA) was positive on day 2, with an optical density index of 2.7, which led to addition of voriconazole (350 mg IV every 12 h) for

suspected invasive pulmonary aspergillosis. An infectious disease consultation was requested and based on her clinical presentation, small yeast forms in BAL and skin, and positive serum GMA EIA, a presumptive diagnosis of disseminated histoplasmosis was made and voriconazole was changed to liposomal amphotericin B (5 mg/kg IV daily) on day 3.

Despite aggressive supportive therapy, the patient died of multiorgan failure on day 7. Serum and urine were tested for *Histoplasma* antigen (collected on day 2) and found to be positive at >39 and 11.57 ng/L, respectively (MVista® *Histoplasma* Quantitative EIA, MiraVista Diagnostics, Indianapolis, Indiana USA). Eventually, the peritoneal fluid, the BAL fluid, and the second skin biopsy grew *H. capsulatum* after 2, 3, and 4 weeks of incubation, respectively. Bone marrow and blood cultures were sterile.

The initial biopsy (left thigh) was reviewed and revealed necrotizing granulomatous panniculitis with septal accentuation; GMS stains did not elucidate any organisms. The subsequent biopsy (right thigh) revealed numerous GMS-positive small budding yeasts without pseudohyphae in a background of panniculitis. Few macrophages appeared to contain organisms.

Discussion

We report a fatal case of PDH presenting with fungal panniculitis in a kidney transplant recipient. Cutaneous involvement is reported in 4–15% of patients with disseminated histoplasmosis, but it was observed in none of 45 cases from 3 recent case series (21–23). *Histoplasma*-associated infective panniculitis is a very rare complication with only 15 compatible cases reported in the literature, including 5 in SOTR (9–20). This case report illustrates the diagnostic challenges of this rare clinical entity, which was misdiagnosed as EN. A detailed literature review identifies specific patterns that could assist clinicians differentiate between EN and infectious (fungal) panniculitis.

Panniculitis is a general term for inflammation of subcutaneous adipose tissue, which is encountered in a wide variety of diseases. EN, an ill-defined type of panniculitis, usually presents with pre-tibial painful, erythematous, non-ulcerating subcutaneous skin nodules of heterogeneous etiologic origin. It has been associated with numerous infectious diseases, including TB and endemic mycoses. The pathophysiology remains poorly understood, but lesions are usually sterile and represent a hypersensitivity reaction to a distant trigger (1). Conversely, infective panniculitis is defined by skin invasion by the pathogen, as seen in uncontrolled disseminated infections (3).

Distinction between the two is critical in an immunocompromised host presenting with EN-like lesions histopathologically described as panniculitis. In SOTR, distinctions in clinical findings between those entities are outlined in prior reports. Gheith et al. (24) described 4 renal SOTR who presented with classical EN. All patients had tender erythematous nodules on anterior aspects of lower limbs, lasting for a few weeks only. Median time of presentation was 35.5 months (range: 20–64 months) after transplantation and all patients were receiving steroid-free maintenance immunosuppression. On the other hand, 5 cases compatible with *Histoplasma* panniculitis in SOTR (all kidney transplants) have been reported in the literature (9–12, 19) (Table 2). The mode of presentation included skin lesions on the trunk and/or arms, alone or along with other sites, but never exclusively on the anterior aspects of the lower extremities, the canonical distribution in EN. This complication occurred earlier after transplantation at a median time of 6 months (range: 6–10 months) and all patients were treated with steroid-containing regimens.

Histopathological description can help establish an accurate diagnosis. Classic EN histomorphology entails nodular septal panniculitis in the absence of vasculitis, while granulomas—except for the distinct Miescher's radial granulomas—and necrosis, are uncommon (25, 26). Necrotizing granulomas are not considered part of the spectrum of findings related to EN (1). In contrast, infective panniculitis is generally considered a lobular panniculitis, although it may exhibit various features depending upon the pathogen (3). Granuloma formation has been described as a remarkable, yet inconsistent feature of fungal panniculitis (3). In the 15 previously reported cases of *Histoplasma* panniculitis (9–20), inflammation was predominantly lobular, septal, and mixed in 2, 3, and 3, respectively; it was not specified in 7 cases. Granulomas were described in 3 cases and necrosis was seen in 3 (all in cases with septal predominance), 2 of which were associated with vasculitis. Thus, lobular or mixed distribution, the presence of granulomas or necrosis, should raise suspicion for infective panniculitis, including *Histoplasma*-associated. However, these findings are neither specific nor sensitive and – alone -- may not be enough to provide a definitive etiologic diagnosis. Specific stains (e.g., acid-fast, silver) and further microbiological investigations may provide crucial additional information. The microbiological diagnosis of histoplasmosis remains challenging, particularly in SOTR, where data are very limited (22, 27–29). Combining data from three large series (22, 27, 29), histopathology and culture (from any site) contributed in the diagnosis of 21/26 (81%) and 34/45 (75%) cases, respectively, but specific data for skin tissue are unavailable. The first biopsy of the present case suggests that the number of organisms may fall under the detection threshold by microscopy. Detection of the *Histoplasma* polysaccharidic antigen (HPA) by EIA is an important adjunct to diagnosis of active disease, with sensitivity in SOTR ranging from 69% to 100% (22, 27, 29). Notably, in disseminated histoplasmosis, sensitivity was found to be comparable with AIDS patients and those with other causes of immunocompromise (28). Data arising from diverse immunocompromised patient groups suggest that the sensitivity of HPA in disseminated histoplasmosis may be comparable in serum and urine, and that the magnitude of antigenuria may correlate with disease severity (23). Interestingly, in the case presented, antigenemia was high and antigenuria detectable despite oliguria. However, these studies were retrospective and included a small number of cases, limiting the ability to draw meaningful conclusions about the performance characteristics of the assays in SOTR. In addition, the GMA EIA is highly cross-reactive to the HPA, also thought to be a galactomannan (30). As illustrated with this case, the GMA EIA may be a useful tool as an adjunct surrogate test for the diagnosis of disseminated histoplasmosis in the appropriate setting, particularly if *Histoplasma* EIA is not readily accessible.

In the case described, the diagnosis was challenging because the initial distribution of lesions and histopathology report pointed to classical EN. The positive IGRA test might have acted as a decoy, as TB is a leading cause of EN even in SOTR (24). In addition, the patient was not from a region considered to be highly endemic for histoplasmosis (31), and the presentation was exceptionally late (it is the most distant case of PDH following SOT, to our knowledge [32]).

However, this case report illustrates the following important points: 1) Biopsy is pivotal in the evaluation of immunocompromised patients presenting with skin lesions (33), and re-biopsy may be necessary in evolving conditions without a clear diagnosis; 2) EN is an exclusion diagnosis that should be re-challenged in the face of an evolving clinical picture; 3) In panniculitis, lobular or mixed distribution and presence of granulomas or necrosis on biopsy should raise suspicion for an infection, including *Histoplasma*-induced panniculitis, even in absence of fungal elements on specific stains; 4) In the presence of extracellular small narrow-budding yeast cells devoid of hyphal elements upon microscopic examination of tissue, histoplasmosis should always be entertained; and 5) When PDH is considered, HPA detection should be performed.

In conclusion, EN-like lesions are a rare but challenging occurrence in the immunocompromised host. Thorough clinical, histopathological, and microbiological investigation is needed in order to diagnose timely and accurately potentially fatal conditions such as PDH.

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Table 1

Summary of pertinent laboratory and microbiology findings

Biochemistry and hematology (upon admission at our hospital)		
Laboratory test	Value	Normal range (unit)
Lactate	7.3	0.5–2.2 (mmol/L)
Urea	86	7–22 (mg/dL)
Creatinine	4.6	0.5–1.2 (mg/dL)
Albumin	1.7	3.5–5.3 (g/dL)
AST	57	0–31 (U/L)
ALT	29	0–31 (U/L)
AlcP	212	30–120 (U/L)
Total bilirubin	0.7	0.1–1.2 (mg/dL)
WBC	12110	4500–11000 (cells/mm ³)
ANC	11989	1500–7800 (cells/mm ³)
ALC	0	1100–4800 (cells/mm ³)
Bands	8	2–6 (%)
Hemoglobin	9.6	12.0–15.0 (g/dL)
Platelets	116000	150–350 (cells/mm ³)
Microbiology and histopathology		
Specimen	Test	Result
Bone marrow *	Stains	Negative
Blood	Culture **	Negative
Serum	GMA EIA	Positive (ODI 2.7)
	HPA EIA	Positive (>39.0 ng/L)
Urine	HPA EIA	Positive (11.57 ng/L)
BAL fluid *	GMS; fungal culture	Small budding yeasts; <i>Histoplasma capsulatum</i> at 3 weeks
	Acid-fast stain; mycobacterial culture	Negative
Transbronchial biopsy *	GMS	Negative
Skin biopsy (#1) *	GMS; culture not done	Negative
Skin biopsy (#2) *	GMS; culture	Small budding yeasts; <i>H. capsulatum</i> at 4 weeks
Peritoneal fluid	Culture	<i>H. capsulatum</i> at 2 weeks

* Analyses performed at the referring hospital.

** Lysis-centrifugation system (Isolator™, Wampole Laboratories, Cranbury, New Jersey USA).

AST, aspartate aminotransferase; ALT, alanine transaminase; AlcP, alkaline phosphatase; WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocytic count; GMA EIA, galactomannan enzyme immunoassay; HPA, *Histoplasma* polysaccharidic antigen; GMS, Grocott's methanamine-silver stain; ODI, optical density index; BAL, bronchoalveolar lavage.

Table 2

Summary of *Histoplasma* panniculitis cases in kidney transplant recipients

Author (ref.)	Demographics: Gender, age in years Location	Time after transplant (months)	Immuno-suppressive regimen	Distribution of skin lesions	Histopathologic findings	Yeast forms on fungal stain	Culture of skin biopsy	Other diagnostic evidence
Dufresne et al. (Present case)	F, 53 Pennsylvania, USA	300	Prednisone, azathioprine	Anterior aspects of legs and arms	Necrotizing granulomatous panniculitis with septal accentuation	No/Yes*	ND/Positive*	BAL fluid, peritoneal fluid (Cx)
Bhowmik et al. (19)	M, 22 India	10	Prednisolone, tacrolimus, MMF	Trunk, thigh	Panniculitis without vasculitis, infiltration of acute inflammatory cells and foamy macrophages	Yes	Positive	Bone marrow (HP)
Daman et al. (12)	M, 52 Tennessee, USA	6	Prednisone, azathioprine	Arms, legs	Panniculitis with a deep-seated granulomatous reaction at the level of eccrine glands and subcutaneous fat	Yes	NS	Blood and sputum (Cx)
King et al. (11)	F, 27 Oklahoma, USA	6	Methylprednisolone, azathioprine	Abdomen, trunk, arms, legs	Granulomatous inflammation of dermis and subcutaneous tissue	Yes	Positive	None
Rifkind et al. (10)	M, 10 Alabama, USA	8	Prednisone, azathioprine, local radiation	Chest	Panniculitis	Yes	ND	Bone marrow (HP, Cx)
Park et al. (9)	M, 12 Georgia, USA	6	Prednisone, azathioprine	Chest, abdomen, thighs	Inflammatory infiltration of subcutaneous fat, with lobules in part replaced by mixed cells (predominantly histiocytes)	Yes	Positive (at autopsy)	Bone marrow (HP, Cx)

* First/second biopsy

M, male; F, female; MMF, mycophenolate mofetil; ND, not done; BAL, bronchoalveolar lavage; HP, histopathology; Cx, culture; NS, not specified.