Petechial, purpuric, and ecchymotic presentation of cutaneous Cryptococcus in mantle cell lymphoma

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INTRODUCTION
Cryptococcus neoformans is an encapsulated, ubiquitous fungus that can infect the skin.1 Cutaneous Cryptococcus usually occurs after dissemination of a respiratory infection but can result from direct contact to the skin.1,3 Although classically seen in HIV-infected patients, cryptococcal infections also occur in HIV-negative individuals with or without other immune deficiencies.1-3 A case of cutaneous Cryptococcus in an HIV-negative patient with mantle cell lymphoma (MCL) is presented to highlight unusual morphologic features that were found.

CASE REPORT
A 71-year-old, HIV-negative white man with MCL was admitted to the hospital with malaise, fatigue, shortness of breath, abdominal pain, hepatosplenomegaly, constipation, and night sweats. After the initial diagnosis of MCL 7 months previously, he received 3 doses of bendamustine-rituximab, each 1 month apart. The MCL did not respond to rituximab, and the patient was started on ibrutinib (560 mg/d) 4 months before admission, which also failed to stall disease progression, prompting another switch of chemotherapeutic agent. Bortezomib infusions on days 1, 4, 8, and 11 were begun 1 month before admission. On the day of admission, the patient came to the hospital to begin his second cycle of bortezomib complaining of a rash of 2 weeks’ duration. He was admitted, and all chemotherapy was held. He was normotensive and afebrile with oxygen saturation of 97%. Physical examination found a slowly expanding, asymptomatic, rash with 10-30 cm patches of dusky erythema studded with 1- to 2-mm purpuric papules that appeared bilaterally on the forearms, antecubital fossae, right side of the neck, right inguinal fold, and lower abdomen. In addition, scattered pin-point petechial and larger ecchymotic macules were present on the upper extremities and trunk (Fig 1). A punch biopsy specimen was obtained from purpuric papules with an erythematous base. One-half was sent for pathologic examination and one-half for bacterial (routine and anaerobes), acid-fast bacilli, and fungal cultures. Encapsulated yeast was identified on hematoxylin-eosin sections (Fig 2). Gomori methenamine silver (Fig 3) and periodic acid–Schiff stained the walls of the yeast. Mucicarmine stained the thick capsules of these organisms. Blood and tissue cultures both grew Cryptococcus. The patient was started on fluconazole, which was escalated to amphotericin B and flucytosine. Despite multiple platelet transfusions, the patient had persistent thrombocytopenia, and he died 2 weeks after admission.

DISCUSSION
Primary cryptococcal infections of the skin are rare and are not usually associated with underlying immune compromise; solitary lesions on uncovered areas such as the hands have occurred in individuals performing outdoor activities in rural areas with exposure to bird droppings.3 Cutaneous
Cryptococcus is most commonly a secondary infection after dissemination of a primary respiratory infection in an immunocompromised individual.\textsuperscript{4} This patient’s immune system was likely compromised by his aggressive lymphoma and chemotherapy treatment. Even when properly treated as in this case,\textsuperscript{5} MCL generally carries a poor prognosis. Cryptococcosis can present with a myriad of cutaneous manifestations. Most commonly, molluscoid, umbilicated or ulcerated papules, nodules, or plaques present with or without background erythema.\textsuperscript{1,6,7} Presentation with asymptomatic petechial, purpurial, or ecchymotic rash is rare although previously described in another thrombocytopenic lymphoma patient. It was postulated that red blood cell extravasation occurred as a result of direct vascular injury by disseminated Cryptococcus.\textsuperscript{8} Compromise of blood vessel walls in combination with thrombocytopenia leads to hemorrhage. Despite a broad differential diagnosis for petechiae and purpura in the setting of lymphoma, this case underscores the importance of considering an atypical presentation of a deep fungal infection.

Early skin biopsy for histopathology and fungal culture is essential in patients in whom disseminated Cryptococcus is suspected, as dermatologic findings can be the presenting sign of this opportunistic infection. Blood cultures should also be performed to identify cryptococccemia. Immediate management of disseminated cryptococcosis may include fluconazole monotherapy (100–400 mg/d) or amphotericin B (0.3–1 mg/kg/d) with or without synergistic flucytosine (75–150 mg/kg/d).\textsuperscript{4} Amphotericin B plus flucytosine is the most effective therapy and is preferred in immunosuppressed patients. Unfortunately, therapy often proves to be ineffective in halting the disease progression if administered too late in the disease course.\textsuperscript{4,7}

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