

Angiolymphoid Hyperplasia with Eosinophilia in a Patient With Coccidioidomycosis

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PRACTICE POINTS

- Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare entity of unknown etiology.
- There is an association between ALHE and coccidioidomycosis (CM). Patients who present with ALHE and reside in a CM-endemic region should be examined for CM.

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare nodular mass that has not commonly been reported in the literature in association with coccidioidomycosis (CM). Coccidioidomycosis has other known skin manifestations including erythema nodosum and interstitial granulomatous dermatitis. Pulmonary CM is the most common form of the disease and the most common cause of CM-associated rash. This is an important clinical consideration for patients with ALHE who reside in CM-endemic areas, which notably include the southwestern region of the United States, Mexico, and South America. We report the case of an ALHE lesion that resolved following treatment for CM.

Cutis. 2022;110:E32-E34.

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare nodular unencapsulated mass that is characterized by benign anomalous vascular hyperplasia of epithelioidlike endothelial cells attached to dilated blood vessels. The mass is surrounded by lymphocytes and eosinophils that can present clinically as papules, plaques, or nodules.¹ The etiology of ALHE is unknown; it is hypothesized that it is a vascular neoplasm or a lymphoproliferative disorder.

Coccidioidomycosis (CM) is a prevalent deep fungal infection endemic to the southwestern United

States caused by *Coccidioides immitis* and *Coccidioides posadasii*. Infection can occur from direct inoculation through abrasions or direct trauma but usually occurs through the inhalation of spores and can result in a reactive rash (eg, Sweet syndrome, erythema nodosum, interstitial granulomatous dermatitis).² Coccidioidomycosis also can result in respiratory pneumonia and dissemination from pulmonary infection of the skin. As such, it is important to distinguish CM and its immunologically mediated eruptions for accurate diagnosis and treatment.

We report a novel case of ALHE as a reactive dermatologic presentation in a patient with CM.

Case Report

A 72-year-old woman presented to the dermatology clinic with itchy papules and plaques on the arms and legs of 17 years' duration. Her medical history included coronary artery disease and hypercholesterolemia as well as a remote history of cutaneous marginal zone B-cell lymphoma of the nose, which was confirmed by histology and treated more than 10 years prior and has remained in remission for 6 years. Her current medications included aspirin, atorvastatin, lisinopril, and metoprolol succinate.

Our patient first presented to our dermatology clinic for itchy nodules and papules on the legs and arms. The patient previously had been seen by another dermatologist 2 months prior for the same condition. At that time, biopsies of the lesions were reported as prurigo nodules. Physical examination at the current presentation revealed round, pink to flesh-colored, raised papules and plaques scattered on the arms and legs (Figure 1). The differential diagnosis included lymphomatoid papulosis, cutaneous B-cell lymphoma, pseudolymphoma, cutaneous CM, and papular mucinosis.

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The authors report no conflict of interest.

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doi:10.12788/cutis.0603

Four-mm punch biopsies of the right proximal pretibial region and left knee region were taken and sent for histologic analysis, direct immunofluorescence testing, and tissue culture. Testing for atypical mycobacteria and deep fungal infection was negative; bacterial cultures and sensitivity testing were negative. Direct immunofluorescence testing was negative. Microscopic examination of material from the right proximal pretibial region showed widely dilated, variously shaped, large blood vessels in a multinodular pattern; the vessels also were surrounded by an inflammatory cell infiltrate containing eosinophils. Histologic findings were consistent with ALHE.

Subsequent biopsies were completed 2 weeks and 1 month from the initial presentation. Both histology reports—from 2 different histopathology laboratories—were consistent with ALHE (Figure 2). Additional work-up during the patient’s initial visit to our clinic for the rash included CM serologic testing, which demonstrated IgM and IgG antibodies. Subsequently, chest radiography revealed a 2.2×2.3-cm mass in the right lower lobe of the lung. Follow-up computed tomography 1 month later confirmed the nodule in the same area to be 2.3×2.1×1.8 cm.

The patient was referred to pulmonology and was treated for pulmonary CM with oral fluconazole 200 mg twice daily for 4 months. Initial treatment also included clobetasol cream 0.05% applied twice daily, which did not produce marked improvement in pruritus. Narrowband UVB phototherapy was attempted, but the patient could not complete the course because of travel time to the office; however, the patient’s ALHE improved considerably with the fluconazole treatment for pulmonary CM.

Oral doxycycline 100 mg twice daily was added to the fluconazole 2 months after her initial visit to our office, which kept the ALHE at bay and helped with the pruritus (Figure 3). Pulmonology and primary care comanaged the pulmonary CM with oral fluconazole 200 mg twice daily. Repeat serologic testing for CM was negative for IgG and IgM after 14 months since the initial visit to the office.



FIGURE 1. Marked angiolymploid hyperplasia with eosinophilia in the right pretibial region at initial presentation.

Comment

Pulmonary CM infection has varying dermatologic manifestations. A PubMed search of articles indexed for MEDLINE using the terms *ALHE* and *coccidioidomycosis* yielded no case reports; in fact, there have been few reported cases of ALHE at all. Notable conditions associated with ALHE include membranous nephropathy and arteriovenous malformations treated with corticosteroids and surgery, respectively.^{3,4} Our case is a rare presentation of CM infection manifesting with ALHE. Following treatment and remission for our patient’s CM infection, the ALHE lesion decreased in size.

Standard treatment of uncomplicated CM involves azole antifungals, typically oral fluconazole or itraconazole 400 to 600 mg/d. In more severe cases (eg, immunocompromised patients) amphotericin B can be used.⁵ Our patient was treated with oral fluconazole 200 mg twice daily for 4 months.

In the literature, treatment via surgical excision, steroid injection, pulsed-dye laser therapy, and radiotherapy also has been described.⁶⁻⁸ Antibiotics including

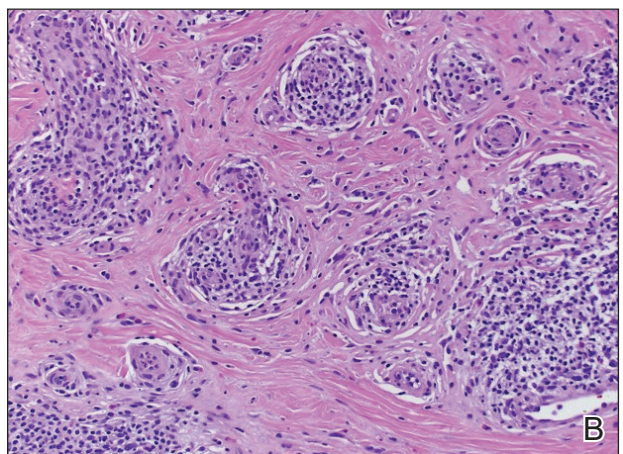
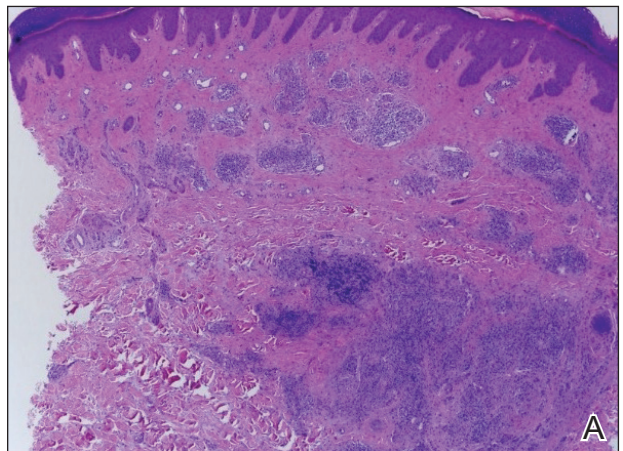


FIGURE 2. A and B, Histologic image of the right proximal pretibial lesion demonstrated a superficial and deep perivascular and interstitial infiltrate with nodular vascularity at low- and high-power views (H&E, original magnifications ×40 and ×100).



FIGURE 3. A clinical photograph taken 5 months after initial presentation showed the results of treatment with fluconazole and doxycycline. The lesions had resolved and there was no pruritus.

clindamycin, doxycycline, and amoxicillin-clavulanate also have been shown to be effective.⁹

In our patient, ALHE improved when oral doxycycline 100 mg twice daily was added to the oral fluconazole. In fact, after 4 months of treatment, the CM infection and ALHE lesions both improved to a point at which the lesions were not visible. When those lesions recurred 15 months later, they responded with another course of doxycycline and fluconazole.

Upon recurrence, the patient was asked to have her care transferred to her pulmonologist, who then managed the fluconazole regimen. During the pulmonologist's workup, no peripheral eosinophilia was found. This is important because eosinophils can be a marker for CM infection; in this case, however, the ALHE lesion was a reactive process to the infection. Classically known to play a reactive role in fungal infection, these white blood cells demonstrate reactivity to the environmental fungus *Alternaria alternata* by contact-dependent killing, utilizing β 2 integrins and CD11b to recognize and adhere to β -glucan. Eosinophils react through contact-dependent killing, releasing cytotoxic granule proteins and proinflammatory mediators, and have been documented to occur in CM and *Paracoccidioides brasiliensis* infection, in which they deposit major basic protein on the organism.¹⁰ Most pertinent to our case with ALHE and CM is the ability of eosinophils to communicate with other immune cells. Eosinophils play a role in the active inflammation of CM through cytokine signaling, which may propagate formation of ALHE.

The function of eosinophils in ALHE is poorly understood; it is unclear whether they act as a primary driver of pathogenesis or are simply indicators of secondary infiltration or infection. Our review of the

current literature suggests that eosinophils are unnecessary for progression of ALHE but might be involved at its onset. As reported, even monoclonal antibody therapy (eg, mepolizumab and benralizumab) that effectively depletes eosinophil levels by negating IL-5 signaling do not slow progression of ALHE.¹¹ Symptomatic changes are modest at best (ie, simply softening the ALHE nodules).

Our patient had no peripheral eosinophilia, suggesting that the onset of ALHE might not be caused by eosinophilia but a different inflammatory process—in this patient, by CM. Because peripheral eosinophilia was not seen in our patient, the presence of eosinophils in the ALHE lesion likely is unnecessary for its onset or progression but is a secondary process that exacerbates the lesion. The pathogenesis is unknown but could be directed toward lymphocytes and plasma cells, with eosinophils as part of the dynamic process.¹¹

Conclusion

Because reports of an association between CM and ALHE are limited, our case is distinguished by a unique clinical presentation of ALHE. When a patient is given a diagnosis of ALHE, it therefore is important to consider exposure to CM as a cause, especially in patients who reside in or travel to a region where CM is endemic.

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