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Review Article

Ecthyma gangrenosum-like lesions caused by *Candida sp.*: A review of literature

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Abstract

Background Ecthyma gangrenosum (EG) is an uncommon, severe, and invasive cutaneous infection typically caused by Pseudomonas aeruginosa. The skin lesion starts off as an erythematous nodule and progresses to a necrotic ulcer with central black eschar. Candida sp. is one of the other species that has been linked to EG-like lesions.

Methods By entering the keywords "Ecthyma gangrenosum" and "Candida" or "Candidal" or "Candidiasis" into PubMed, this review of the literature was conducted. The outcomes were not subjected to any filters or limitations on language.

Results Eight studies and nine cases with EG-like lesions connected to Candida sp. were evaluated and were available on PubMed between 1979 and 2016. One of the nine case reports had neonates as young as 12 days old, while the others in age from 21 to 69. Numerous case reports have used the culture in addition to the biopsies. Pseudohyphae or budding yeast were found in seven out of nine instances of histopathology. Three out of 9 cases reported as disseminated candidiasis.

Conclusions A candida infection, especially disseminated candidiasis, should be included in the differential diagnosis of an immunocompromised patient who shows necrotic lesions that mimic EG and be verified by biopsy as well as culture.

Key words
Ecthyma gangrenosum-like lesions; Ecthyma gangrenosum, *Candida sp*.; Disseminated candidiasis; Pseudomonas aeruginosa.

Introduction

Ecthyma gangrenosum (EG) is a severe and invasive cutaneous infection that occurs rarely. It is typically brought on by *Pseudomonas aeruginosa*, which is frequently present in immunocompromised people.[1,2] The skin lesion commonly presents as an erythematous nodule that develops into a necrotic ulcer with a central black eschar formation.[1] The lesion of EG predominantly appears in the axillary and anogenital areas, followed by the arms, legs, trunk, and face.[1,3] Necrotic lesions resembling EG can have various microbiological etiologies. Other species known to cause lesions similar to EG include *Escherichia coli, Klebsiella pneumoniae, Streptococcus spp., Citrobacter freundii, Morganella morganii, Stenotrophomonas maltophilia, Proteus sp., Serratia marcescens, Vibrio vulnifucus, Aeromonas hydrophila, Staphylococci, Streptococcus pyogenes,* and *Neisseria gonorrhoeae.* Additionally, various fungi, *such as Candida sp., Aspergillus sp., Curvularia,*

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Mucor, Fusarium solani, and Scytalidium dimidiatum, have been observed to cause comparable lesions.[4-6] For a definitive diagnosis, blood cultures and skin biopsies with cultures are required. Any isolated organisms are subjected to sensitivity tests. Aggressive antibiotic or antifungal treatment is recommended once the etiology is identified, but because EG presents as a necrotizing soft-tissue lesion, surgical excision is frequently required.[7] In this article, we review the cases of EG-like lesions caused by *Candida sp.*

This literature review was performed on PubMed by submitting the key words "Ecthyma gangrenosum" and "Candida" or "Candidal" or "Candidiasis". No filters or language restrictions were applied to the results. A total of eight papers, consisting of nine case reports, were selected for review. An article was considered eligible for inclusion if it reported cases with full clinical data consistent with EG-like lesions caused by *Candida sp*. The following epidemiologic and clinical variables were evaluated for each case: gender, age, clinical manifestations, antifungal therapy, surgical procedures, and clinical outcome. The outcome was considered good in patients who responded to treatment and did not present with sequelae.

Methods

The authors reviewed eight articles regarding EG-like lesions associated with *Candida sp*. infections that were published on PubMed between 1979 and 2016 **(Table 1)**. One of the eight articles presents two case reports simultaneously. In one of the nine case reports, newborns as young as 12 days old were found to have EG with *Candida sp.* infection, while the other eight patients ranged in age from 21 to 69 years old with a male-to-female ratio of 4:5. Felty's syndrome, acute erythroleukemia, nonseminomatous germ cell tumor, protein energy malnutrition, multiple myeloma, ischemic heart disease, acute myeloid leukemia, anemia, and Castleman disease were found to be comorbidities in reported cases. The cutaneous manifestations in all of the patients were necrotic ulcers with a blackish eschar development in the center and an erythematous halo surrounding the ulcers, despite the fact that each patient's chief complaint was different when they arrived at the hospital. In addition to the biopsy, the culture was used in a number of case reports. Of the nine case reports, one case performed a blood culture, six cases performed a skin lesion culture, two cases used Sabouraud Dextrose Agar (SDA) medium and one used Lowenstein medium to culture, whereas the other two cases performed urine cultures and bone marrow aspirations. Of the nine cases that were reported, *P. aeruginosa* and *C. tropicalis* infections were identified in one case, *P. aeruginosa* and *C. albicans* infections in one case, and *P. vulgaris* and *C. albicans* infections in one case. Seven of nine cases had pseudohyphae or budding yeast on histopathology. To the best of our knowledge, three out of nine cases reported as disseminated candidiasis while others reported as ecthyma gangrenosum caused by *Candida sp*.[2,8-14]

Patients diagnosed with EG due to *Candida sp.* were then given antifungal therapy. Two cases continued therapy with surgical debridement to remove the necrotic tissue. After carrying out several treatments, it was reported that four cases improved (two cases improved in 4 weeks, one case in 5 weeks, and the other one improved in 3 weeks), three cases died (two of them due to cardiac arrest), and two cases were lost to follow-up.

Discussion

Ecthyma gangrenosum (EG) is a form of necrotizing vasculitis that usually occurs in

Table 1 Case reports of patients with ecthyma gangrenosum-like lesions caused by *Candida sp*.

First Author (Year)	*Under- lying Disease*	*Chief Complaint*	*Skin manifestation*	*Cultures*				*Histo-pathology*	*Treatment*	*Outcome*
				Blood	*Lesion*	*Medium*	*Bone marrow aspirate/ urine*			
File, TM (1979) [8]	A 69-year-old woman with Felty's syndrome	Comatose	Tender necrotic lesions → well-demarcated eschar with surrounding induration and erythema	*P. aeruginosa*	*C. tropicalis* +, *P. aeruginosa* -	N/A	Bone marrow aspirate, urine, multiple blood cultures: *C. tropicalis* +, *P. aeruginosa* -	GMS stain: yeast and pseudohyphae within dermis.	Flucytosine 150 mg/kg/day by mouth and amphotericin B 1 mg IV → discontinued the flucytosine and increased the Amphotericin B dosage to 1 mg/kg/day for 28 days	Died of cardiac arrest (autopsy was not granted)
Fine, JD (1981)[9]	A 21-year - old Cuban man with acute erythroleukemia	Admitted to the hospital for evaluation and treatment of leukemia.	A left inguinal ulcer with bilateral inguinal lymphadenopathy.	*P. aeruginosa*	*P. aeruginosa*	N/A	A bone marrow aspirate: acute leukemia Urine: *P. aeruginosa*	HE stain: Pseudohyphae fill the papillary dermis and extend into the overlying epidermis.	Amphotericin B	Died of cardiac arrest (autopsy confirmed disseminated candidiasis involving liver, lungs, spleen).
Leslie, KS (2005)[10]	A 68-year-old man with protein energy malnutrition	4 week history of swollen red leg with the development of the ulcers Fever (-)	Widespread erythema and oedema with multiple areas of necrotic ulceration, eschar formation, and some pustules.	Negative	*C. albicans*	N/A	N/A	PAS stain: Superficial focus of inflammation containing *Candida*, dermis was fibrotic and showed a mixed inflammatory infiltrate of lymphocytes, plasma cells and neutrophils.	Oral itraconazole 100 mg once daily for 4 weeks.	Improved in 5 weeks
Agarwal, S (2006)[11]	A 12-day-old female neonate	Progressive black lesion below the left lower eyelid began from the 3rd day of life.	A single, large, well defined, irregular margin, indurated with central black eschar on the left lower eyelid and on left parieto-	Sterile	Negative	SDA medium: *C. albicans*	N/A	PAS stain: PAS positive candidal pseudohyphae. Pus on gram stain: Gram positive budding	Topical antifungal cream + systemic Fluconazole + surgical debridement + drainage pus	Improved in 4 weeks

First Author (Year)	*Under- lying Disease*	*Chief Complaint*	*Skin manifestation*	*Cultures*				*Histo-pathology*	*Treatment*	*Outcome*
				Blood	*Lesion*	*Medium*	*Bone marrow aspirate/ urine*			
		Fever (+), diarrhea (+)	temporal region of face.					yeast cells, pseudohyphae and pus cells.		
Obasi, OE (2007)[12]	A 64-year-old female with multiple myeloma	6-week-history of painful ulcers with blister formation on both feet and ankles.	Multiple ulcers covered with a thick gray-black crust, slight erythematous halo and thin superficial blisters on the anterior ankles and dorsum of feet.	N/A	*C. albicans*	N/A	Urine: *C. albicans*	N/A	N/A	Lost to follow up
Soria, A (2010)[13]	A 60-year-old man, heart transplant recipient for ischemic heart disease	Fever (+), cough (+), dyspnea (+)	Swelling of the posterior surface of the left calf gradually increasing in size, necrotic then secondary ulceration for several weeks, painless	Negative	N/A	Lowenstein medium: *C. albicans*	Urine: sterile	Direct examination: pseudo-mycelial filaments	Fluconazole for 4 weeks (until total regression of abscesses).	Improved in 4 weeks
	A 54-year-old woman with type 2 acute myeloid leukemia	Right axilla skin lesion Fever (+)	Bullous skin lesion in right axilla evolved into a blackish crust approximately 1.5 cm in diameter, very well limited, sitting on a hot and infiltrated erythematous plaque, accompanied by right axillary adenopathy.	*P. aeruginosa*	*C. albicans*	SDA medium: *C. albicans*	N/A	N/A	Fluconazole was associated with antibiotic therapy	Died
Lee YJ (2015)[14]	A 57-year-old woman with castleman disease	Multiple skin lesions involving her trunk and upper extremities. Fever (+)	Deep punched-out ulceration on the abdomen near the colostomy site + a large, palm-sized eschar formation with an erythematous halo on right arm involving trunk and upper extremities.	N/A	*P. vulgaris* +, *C. albicans* +	N/A	N/A	Gram-stain: *P. vulgaris*	Ceftazidime and teicoplanin with fluconazole + surgical debridement	Improved in 3 weeks

First Author (Year)	*Under- lying Disease*	*Chief Complaint*	*Skin manifestation*	*Cultures*				*Histo-pathology*	*Treatment*	*Outcome*
				Blood	*Lesion*	*Medium*	*Bone marrow aspirate/ urine*			
Beasley, K (2016)[2]	A 24-year - old male with stage IV non-seminomato us germ cell tumor	Rash on bilateral lower extremities, lower abdomen and flanks one Fever (+)	Diffusely scattered erythemato us papules on bilateral lower extremities + non palpable purpura involving the lower abdomen and flanks → progressed into large hemorrhagic bullae that become necrotic stellate ulcers.	*C. tropicalis*	*C. tropicalis*	N/A	N/A	PAS stain : Suppurative granulomatous inflammation in dermis & subcutis GMS stain: budding yeast in dermis	Amphotericin B and micafungin → fluconazole monotherapy once the speciation of *C. tropicalis* was determined + debrided 125 cm2 of necrotic tissue from left lower extremity → voriconazole + amphotericin B due to a new pulmonary nodule concerning for fungal versus metastatic disease → amphotericin B stopped once voriconazole reached a therapeutic level.	Lost to follow up

immunocompromised individuals.[1,2] It is caused by an organism occluding blood vessels, with Pseudomonas aeruginosa being the most frequently reported etiology. Though it happens rarely, bacteremia can occasionally be absent in some cases.[15,16] Predisposing factors include neutropenia, malignancy, burns, malnutrition, and tuberculosis.[17] It is important to identify any underlying hematological abnormalities, including variants of neutropenia such as chronic, cyclic, and transient neutropenia, the last of which is most commonly reported in association with EG.[7] Lesions typically start as painless gunmetal gray macules or papules with erythema surrounding them and progress to ecthyma. The lesion then becomes more indurated, pustules or hemorrhagic bullae develop, and eventually, necrotic ulcerative eschars are formed, surrounded by an erythematous halo.[15,11] This lesion represents a major skin sign of an underlying potentially life-threatening systemic infection.[11] Histologically, organisms can be seen in the media and adventitia of vascular walls, which may eventually occlude the vessel and result in clinical eschar.[2]

Disseminated candidiasis is frequent and causes serious complications in immunocompromised patients. The most frequent Candida species was *C. tropicalis* (68%), followed by *C. krusei* (15%) and *C. albicans* (10%).[2,18] The lesion usually appears as erythematous papules and nodules with central postulation.[19] A distinctive triad of high fever, papular erythematous skin lesions, and diffuse muscle tenderness has been proposed as a diagnostic clue in disseminated candidiasis.[2] It could be clinically similar to an EG.[8,9] According to Argawal, a fungal infection, including *Candida sp.*, may also cause EG-like lesions.[11] Based on File's case report, the macroscopic features of the reported necrotic skin lesions were similar to those of ecthyma gangrenosum and were distinct from the cutaneous nodules of disseminated candidiasis that are smaller (less than 1 cm in diameter) and nonnecrotic.[8] However, a biopsy specimen's histological characteristics were comparable to the nodular lesions of disseminated candidiasis, including an infiltration of the dermis with yeast and pseudohyphae typical of invasive candidiasis.[8]

Early diagnosis of these infections is sometimes difficult, and blood cultures frequently yield negative results.[9] A KOH preparation or gram stain of the material from the involved area of skin, along with a skin biopsy, blood or lesion culture, and a special stain for fungal species, can be used to confirm the diagnosis in such cases.[11,19] Without obtaining a biopsy, *Pseudomonas* would have been presumed, and candidiasis may have only been discovered at postmortem, according to Fine. Although skin involvement by disseminated candidiasis is uncommon, this diagnosis should be taken into consideration when nodules and lesions that resemble ecthyma gangrenosum develop in an immunocompromised host.[8,9,11]

Treatment of a disseminated *C. tropicalis* infection typically involves either amphotericin B or an azole. In a study of 125 *C. tropicalis* isolates, amphotericin B has the lowest resistance rate at 17.6%, followed by itraconazole (67.2%), ketoconazole (68%), and fluconazole (71.2%).[5] Increased resistance to fluconazole was noted in *C. tropicalis* that has been isolated from blood cultures, and the organism was able to form a biofilm. In addition to medical therapy, debridement is also an important form of source control, as the patient can have persistent positive wound cultures despite days of antifungal treatment.[2] From the 9 cases reported, 4 cases improved on average after 4 weeks of antifungal treatment, while 3 cases died and 2 cases were lost to follow-up.

Conclusion

Ecthyma gangrenosum has traditionally been associated with *Pseudomonas* infections; however, a fungal infection, such as *Candida sp.*, can also cause EG-like lesions. In an immunocompromised patient presenting with nodules and necrotic lesions that resemble EG, a candida infection, including disseminated candidiasis, should be included in the differential diagnosis and confirmed by biopsy as well as culture.

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