Iododerma Simulating Cryptococcal Infection

Abraham Moris Korman, MD; Jose A. Plaza, MD; Benjamin H. Kaffenberger, MD

PRACTICE **POINTS**

- Halogenodermas are rare cutaneous reactions to excess exposure to or ingestion of halogen-containing drugs or substances such as bromine, iodine (iododerma), fluorine, and rarely lithium.
- The clinical presentation of a halogenoderma varies; the most characteristic manifestation is a vegetative or exudative plaque with a peripheral rim of pustules.
- Histologically, lesions of a halogenoderma are characterized by pseudoepitheliomatous hyperplasia associated with numerous intraepidermal microabscesses overlying a dense mixed inflammatory infiltrate of neutrophils, plasma cells, eosinophils, histiocytes, and scattered multinucleated giant cells.
- Rarely, the dermal infiltrate of a halogenoderma contains abundant acellular bodies surrounded by capsulelike vacuolated spaces mimicking *Cryptococcus neoformans.*

To the Editor:

A woman in her 40s presented with acute onset of rapidly spreading lesions on the face, trunk, and extremities. She reported high fever and endorsed malaise. She had a history of end-stage renal disease and was on renal dialysis. She recently underwent revision of an arteriovenous fistula.

Physical examination revealed diffuse, erythematous, firm papules and plaques with central hemorrhage and umbilication on the dorsal aspect of the nose, forehead, temples, and cheeks. There also were purpuric papules and plaques with a peripheral rim of vesiculation (Figure 1) on the medial and posterior thighs and buttocks. Histopathology of a biopsy specimen revealed an interstitial neutrophilic infiltrate in the superficial dermis and mid dermis with scattered, haloed, acellular structures simulating cryptococcal organisms (Figure 2). Periodic acid–Schiff (PAS), Grocott methenamine-silver, and mucicarmine staining was negative. Repeat biopsy showed similar findings. A (1-3)-β-D glucan assay for invasive fungal infection and tests for serum cryptococcal antigen, serum *Coccidioides* antibody, serum *Blastomyces* antigen, and urine and serum *Histoplasma* antigen were negative. A fungal complement fixation battery was negative. Blood and tissue cultures for bacteria, anaerobes, fungi, and acid-fast bacilli remained sterile. Swabs were negative for varicella-zoster virus and herpes simplex virus. Urine and blood iodine levels were 344,998 μg/L (reference range, 34–523 μg/L) and 47,459 μg/L (reference range, 52–109 μg/L), respectively. The elevated iodine levels were presumed to be secondary to iodinated contrast media that the patient received for revision of the arteriovenous fistula.

The findings compatible with a diagnosis of iododerma included umbilicated hemorrhagic papules and plaques, cryptococcal-like structures with negative staining on histopathology, and elevated iodine levels with a negative infectious workup. The patient was treated with topical corticosteroids. At 1-month follow-up, the lesions had resolved.

Iododerma is a halogenoderma, a skin eruption that occurs after ingestion of or exposure to a halogen-containing substance (eg, iodine, bromine, fluorine) or medication

From The Ohio State University, Columbus. Drs. Korman and Kaffenberger are from the Department of Dermatology, and Dr. Plaza is from the Department of Pathology.

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Correspondence: Abraham Moris Korman, MD, 540 Officenter Center Pl, Ste 240, Columbus, OH 43230 (Abraham.Korman@osumc.edu).

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(eg, lithium).[1] Common sources of iodine include iodinated contrast media, potassium iodide ingestion, topical application of povidone–iodine, radioactive iodine administration, and the antiarrhythmic amiodarone. Excess exposure to iodine-containing compounds typically occurs in the setting of kidney disease or failure as well as due to reduced iodine clearance.[1] Although the pathogenesis of iododerma is unknown, the most common hypothesis is that lesions are delayed hypersensitivity reactions secondary to formation of a protein-halogen complex.[2]

The presentation of iododerma is polymorphous and includes acneform, vegetative, or pustular eruptions; umbilicated papules and plaques can be present.[2,3] Lesions can be either asymptomatic or painful and pruritic. Timing between iodine exposure and onset of lesions varies from hours to days to years.[2,4]

Systemic symptoms of iododerma can occur, including salivary gland swelling, hypotension and bradycardia, kidney injury, or thyroid and liver abnormalities. Histopathologic analysis demonstrates a dense neutrophilic dermatitis with negative staining for infectious causes.[4,5] Cryptococcal-like structures have been described in iododerma[3]; neutrophilic dermatoses of various causes that mimic cryptococcal infection have been reported.[6] Ultimately, iododerma remains a diagnosis of exclusion.

Withdrawal of an offending compound is remedial. Dialysis is beneficial in end-stage renal disease. Topical, intralesional, and systemic corticosteroids, as well as antibiotics, provide variable benefit.[4,7] Lesions can take 4 to 6 weeks to clear after withdrawal of the offending agent. It is unclear whether recurrences happen; iodine-containing compounds need to be avoided after a patient has been affected.

Iododerma has a broad differential diagnosis due to the polymorphous presentation of the disorder, including acute febrile neutrophilic dermatosis (also known as Sweet syndrome), cutaneous cryptococcosis, and cutaneous histoplasmosis. Sweet syndrome presents as abrupt onset of edematous erythematous plaques with fever and leukocytosis. It is associated with infection, inflammatory disorders, medication, and malignancy.[8] Histopathologic analysis reveals papillary dermal edema and a neutrophilic dermatosis. Cytoplasmic vacuolization resembling *C neoformans* has been reported.[9] The diagnosis is less favored in the presence of renal disease, temporal association of the eruption with iodine exposure, and elevated blood and urine iodine levels, as in our patient.

Cutaneous cryptococcosis, an infection caused by *C neoformans*, typically occurs secondary to dissemination from the lungs; rarely, the disease is primary. Acneform plaques, vegetative plaques, and umbilicated lesions are seen.[10] Histopathologic analysis shows characteristic yeast forms of cryptococcosis surrounded by gelatinous edema, which create a haloed effect, typically throughout the dermis. Capsules are positive for PAS or mucicarmine staining. Although *C neoformans* can closely mimic iododerma both clinically and histopathologically, negative infectious staining, localization of haloed structures to the upper dermis, a negative test for cryptococcal antigen, and elevated blood and urine iodine levels in this case all favored iododerma.

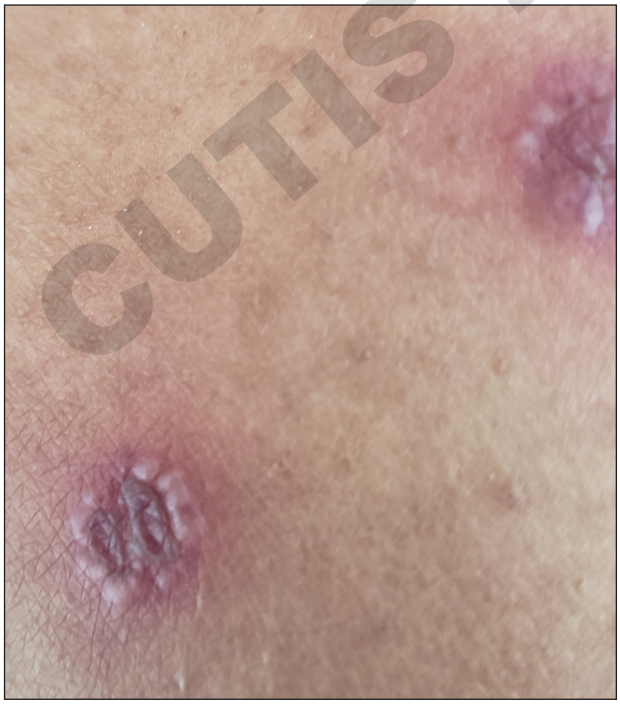

FIGURE 1. Purpuric plaques on the thigh with peripheral vesiculation.

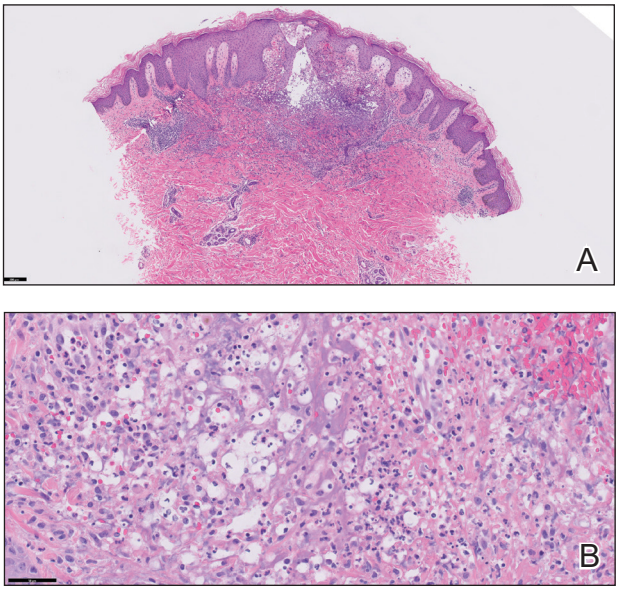

FIGURE 2. A, Histopathology showed interstitial superficial and mid-dermal neutrophilic dermatitis with focal subepidermal edema (H&E, original magnification ×10). Reference bar indicates 200 µm. B, At higher magnification, scattered, haloed, cryptococcal-like structures were seen that were negative for periodic acid–Schiff, Grocott methenamine-silver, and mucicarmine staining (H&E, original magnification ×20). Reference bar indicates 50 µm.

Cutaneous histoplasmosis is an infection caused by *Histoplasma capsulatu*m, most commonly as secondary dissemination from pulmonary infection but rarely from direct inoculation of the skin.[11] Presentation includes erythematous to hemorrhagic, umbilicated papules and plaques. Histopathologic findings are round to oval, narrow-based, budding yeasts that stain positive for PAS or mucicarmine. Although histoplasmosis can clinically mimic iododerma, the disease is distinguished histologically by the presence of fungal microorganisms that lack the gelatinous edema and haloed effect of iododerma.

We presented a unique case of iododerma simulating cryptococcal infection both clinically and histopathologically. Prompt recognition of histologic mimickers of true infectious microorganisms is essential to prevent unnecessary delay of withdrawal of the offending substance and to initiate appropriate therapy.

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