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Localized calcium oxalate crystals in primary cutaneous aspergillosis

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Abstract

Select *Aspergillus* species can produce oxalate as a fermentation byproduct, which may react with calcium ions to produce insoluble calcium oxalate crystals in tissues. These crystals are frequently associated with pulmonary *Aspergillus* infections, yet are rarely described in primary cutaneous aspergillosis. Herein, we report the presence of calcium oxalate crystals detected on cutaneous specimens from primary cutaneous *Aspergillus niger* and *Aspergillus fumigatus* infections in an immunocompromised, premature infant. No metabolic sources of oxalosis were found.

Keywords

oxalosis; calcium oxalate crystals; primary cutaneous aspergillosis; Aspergillus

Introduction

Select *Aspergillus* species produce oxalic acid, which may compound with calcium at physiological pH forming calcium oxalate crystals in affected tissues.[1] *Aspergillus* species that produce oxalic acid include *A. fumigatus*, *A. flavus*, and *A. niger*, with *A. niger* being the most common *Aspergillus* species associated with oxalosis.[2,3] In particular, calcium oxalate crystals frequently appear in pulmonary aspergillosis and its presence in pulmonary cytology specimens is often used to make the diagnosis in cases that lack confirmatory

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histopathology results or fungal cultures.[2-4] However, they are rarely described in primary cutaneous *Aspergillus* infections.[5,6]

Primary cutaneous aspergillosis is a rare opportunistic infection that occurs through direct skin inoculation of fungal spores, primarily affecting immunocompromised individuals.[7] *A. flavus* is the most common causative organism in immunocompromised hosts, while *A. niger* and *A. fumigatus* are more common among healthy individuals.[5] Characteristic lesions begin as erythematous, indurated plaques that progress to necrotic, black eschars. The prognosis of primary cutaneous aspergillosis is often grim in immunocompromised individuals, highlighting the importance of prompt identification and treatment.

Herein, we report a case of primary cutaneous *A. niger* and *A. flavus* infections in an immunocompromised infant presenting with a cutaneous eruption with localized calcium oxalate deposition visualized on histopathology, suggesting that the presence of calcium oxalate in cutaneous specimens may assist in identifying oxalate-producing *Aspergillus* species infections.

Case presentation

Dermatology was consulted to evaluate a rash on the back of a critically ill, nine-day old female born prematurely at 22 weeks. The patient was admitted for management of respiratory insufficiency requiring intubation after birth, spontaneous intestinal perforation status post peritoneal drain placement, bilateral intraventricular hemorrhage, and septic shock secondary to *Enterococcus faecalis* bacteremia treated with broad-spectrum antimicrobials. The patient's mother was immunocompetent with no evidence of infection prior to delivery.

Dermatological examination was significant for multiple, irregularly shaped, coalescing eroded plaques with overlying dry, yellow-grey, and hemorrhagic crust on the mid and upper back. Few similar scattered lesions were distributed on the extremities (Figure 1A). Opportunistic infections such as fungal were initially considered given the patient's immunocompromised status as a premature infant. Liposomal amphotericin B was therefore initiated for broad fungal coverage. HSV/VZV PCR was negative.

Histological examination of a punch biopsy specimen taken from the patient's back revealed ulcerated skin with abundant superficial, radially-oriented needle-shaped birefringent crystals identified as calcium oxalate (Figure 2-3). Inflammatory infiltrates with sparse eosinophils were present. Periodic acid–Schiff–diastase (PAS-D), Gram, and Fite stains were negative for fungal, bacterial, or mycobacterial pathogens, respectively. Lesional crust was subsequently sent for pathology, which revealed septate hyphae with acute angle branching, consistent with primary cutaneous aspergillosis (Figure 4). Metabolic work up for causes of oxalosis was completed. Urine quantitative organic acid test detected the presence of oxalic and glycolic acids. The patient had a normal creatine and did not show evidence of primary or secondary hyperoxaluria. Follow up wound and tissue cultures obtained from the back confirmed *A. niger, A. flavus*, and *Enterococcus faecalis*.

Work-up for a disseminated fungal infection (echocardiogram, ophthalmology evaluation, abdominal ultrasound, and lumbar puncture) was negative. The patient was continued on liposomal amphotericin B and ampicillin until the rash resolved 40 days later (Figure 1B).

Discussion

Herein, we describe a case of localized cutaneous calcium oxalate deposition in primary cutaneous *A. niger* and *A. flavus* infection in an immunocompromised infant. Histological examination revealed superficial calcium oxalate crystals and subsequent specimen of superficial crust and cultures confirmed *Aspergillus* infection. This suggests that the presence of calcium oxalate crystals in skin specimens may be a diagnostic clue for *Aspergillus* infections, particularly when the clinical suspicion is high.[2,10]

Oxalate-producing *Aspergillus* species can give rise to calcium oxalate crystals in tissues and cytologic specimens.[2] Calcium oxalate crystals are yellow to brown, radially arranged, predominantly needle-shaped or rectangular, and strongly birefringent under polarized light.[2,9,17] [2,3] While this finding commonly occurs in pulmonary aspergillosis, only two cases have reported its presence in primary cutaneous *Aspergillus* infections.[5,6] These reports described immunocompromised adult males presenting with gangrenous limbs, both complicated by *A. niger* infections while one had simultaneous mucormycosis. Both patients required amputations, and one case resulted in death. Pathologic specimens in both cases revealed strongly birefringent crystals identified as calcium oxalate crystals. Isolated case reports have also described calcium oxalate crystals in a maxillary sinus fungal ball[8] and necrotizing otomycosis[9] secondary to *A. nidulans* and *A. niger* infections, respectively.

There is increasing evidence suggesting that calcium oxalate crystals in *Aspergillus* infections potentiate the destructive nature of the fungus and may be associated with a poorer prognosis.[2] Many reported *Aspergillus* cases with calcium oxalate deposition highlight the severe and occasionally life-threatening effects of these crystals.[5,18-21] Experimental studies have shown that calcium oxalate crystals induce cellular injury by causing lipid peroxidation and inducing enzyme release from polymorphonuclear leukocytes.[22-25]

Other causes of tissue oxalosis should be investigated when calcium oxalate crystals are identified on pathologic specimens. Primary hyperoxaluria is a rare inherited error of metabolism caused by a defective enzyme that normally prevents the overproduction of oxalate, resulting in recurrent kidney stones and chronic kidney disease. Conversely, secondary hyperoxaluria is caused by the consumption of oxalate-rich foods, or by intestinal diseases that cause increased oxalate absorption, such as Crohn's disease and short bowel syndrome. Additionally, since oxalate is renally excreted, renal insufficiency may also result in systemic oxalosis. Renal oxalosis has also occurred in cases of pulmonary aspergillosis.[11,12] Our patient's hyperoxaluria was presumed to be a result of the *Aspergillus* infection since it resolved with antifungal treatment and there was no evidence of metabolic oxalosis or renal insufficiency.

Tissue oxalosis is not common in other isolated cutaneous infections. A single case of pulmonary mucormycosis associated with calcium oxalate and calcium carbonate crystals has occurred.[13] Additionally, multiple cases of mucormycosis panniculitis,[14] and a single case of cutaneous *A. flavus* infection[15] have been described in association with necrotic adipocytes filled with radially-oriented, needle-shaped, monosodium urate crystals.[16] Although urate and calcium oxalate crystals can have a similar appearance in skin specimens, the negative birefringence of urate crystals compared to the positive birefringence of calcium oxalate crystals are helpful distinguishing features.

In conclusion, the presence of calcium oxalate crystals in cutaneous specimens may support a diagnosis of cutaneous aspergillosis in the absence of other oxalosis-associated disorders. Clinicopathologic correlation is required, but this histopathologic finding my cue providers into earlier diagnosis and treatment.

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References

1. Li C, Li Q, Wang Z, et al. Environmental fungi and bacteria facilitate lecithin decomposition and the transformation of phosphorus to apatite. Sci Rep. 2019;9(1):15291. [PubMed: 31653926]
2. Pabuççuoğlu U. Aspects of oxalosis associated with aspergillosis in pathology specimens. Pathol Res Pract. 2005;201(5):363–368. [PubMed: 16047945]
3. Reyes CV, Kathuria S, MacGlashan A. Diagnostic value of calcium oxalate crystals in respiratory and pleural fluid cytology. A case report. Acta Cytologica. 1979;23(1):65–68. [PubMed: 285553]
4. Farley ML, Mabry L, Munoz LA, Diserens HW. Crystals occurring in pulmonary cytology specimens. Association with Aspergillus infection. Acta Cytologica. 1985;29(5):737–744. [PubMed: 3863422]
5. Louthrenoo W, Park YS, Philippe L, Schumacher HR Jr. Localized peripheral calcium oxalate crystal deposition caused by Aspergillus niger infection. Journal of Rheumatology. 1990;17(3):407–412. [PubMed: 2185361]
6. Reyes CV, Rippon JW. Localized oxalosis associated with simultaneous Aspergillus and Mucor infection in diabetic foot gangrene. Human Pathology. 1984;15(1):89–91. [PubMed: 6693115]
7. Estes SA, Hendricks AA, Merz WG, Prystowsky SD. Primary cutaneous aspergillosis. J Am Acad Dermatol. 1980;3(4):397–400. [PubMed: 6776166]
8. Kimura M, Enomoto A, Maenishi O, Chikugo T, Sugita T. A fungal ball within a maxillary sinus with dental root canal filler and rare fungal propagules. Pathol Int. 2019;69(6):360–365. [PubMed: 31215141]
9. Landry MM, Parkins CW. Calcium oxalate crystal deposition in necrotizing otomycosis caused by Aspergillus niger. Modern pathology. 1993;6(4):493–496. [PubMed: 8415598]
10. Ghio AJ, Peterseim DS, Roggli VL, Piantadosi CA. Pulmonary oxalate deposition associated with Aspergillus niger infection. An oxidant hypothesis of toxicity. The American review of respiratory disease. 1992;145(6):1499–1502. [PubMed: 1596026]
11. Vaideeswar P, Sakhdeo UM. Pulmonary aspergilloma with renal oxalosis: fatal effect at a distance. Mycoses. 2009;52(3):272–275. [PubMed: 18643917]

12. Roehrl MH, Croft WJ, Liao Q, Wang JY, Kradin RL. Hemorrhagic pulmonary oxalosis secondary to a noninvasive Aspergillus niger fungus ball. Virchows Arch. 2007;451(6):1067–1073. [PubMed: 17786471]
13. Rassaei N, Shilo K, Lewin-Smith MR, Kalasinsky VF, Klassen-Fischer MK, Franks TJ. Deposition of calcium salts in a case of pulmonary zygomycosis: histopathologic and chemical findings. Hum Pathol. 2009;40(9):1353–1357. [PubMed: 19454361]
14. Requena L, Sitthinamsuwan P, Santonja C, et al. Cutaneous and mucosal mucormycosis mimicking pancreatic panniculitis and gouty panniculitis. J Am Acad Dermatol. 2012;66(6):975–984. [PubMed: 21958652]
15. Colmenero I, Alonso-Sanz M, Casco F, Hernández-Martín A, Torrelo A. Cutaneous aspergillosis mimicking pancreatic and gouty panniculitis. J Am Acad Dermatol. 2012;67(4):789–791.
16. Vernon SE, Dave SP. Cutaneous zygomycosis associated with urate panniculitis. Am J Dermatopathol. 2006;28(4):327–330. [PubMed: 16871036]
17. Kurrein F, Green GH, Rowles SL. Localized deposition of calcium oxalate around a pulmonary Aspergillus niger fungus ball. Am J Clin Pathol. 1975;64(4):556–563. [PubMed: 1199978]
18. Kimmerling EA, Fedrick JA, Tenholder MF. Invasive Aspergillus niger with fatal pulmonary oxalosis in chronic obstructive pulmonary disease. Chest. 1992;101(3):870–872. [PubMed: 1541168]
19. Kurrein F, Path FRC, Green GH, Rowles SL. Localized deposition of calcium oxalate around a pulmonary Aspergillus niger fungus ball. American Journal of Clinical Pathology. 1975;64(4):556–563. [PubMed: 1199978]
20. Metzger JB, Garagusi VF, Kerwin DM. Pulmonary oxalosis caused by Aspergillus niger. American Review of Respiratory Disease. 1984;129(3):501–502. [PubMed: 6703507]
21. Nakagawa Y, Shimazu K, Ebihara M, Nakagawa K. Aspergillus niger pneumonia with fatal pulmonary oxalosis. Journal of Infection and Chemotherapy. 1999;5(2):97–100. [PubMed: 11810498]
22. Elferink JGR, Deierkauf M. Enzyme release from polymorphonuclear leukocytes during interaction with calcium oxalate microcrystals. Journal of Urology. 1987;138(1):164–167. [PubMed: 2439709]
23. Thamilselvan S, Hackett RL, Khan SR. Lipid peroxidation in ethylene glycol induced hyperoxaluria and calcium oxalate nephrolithiasis. Journal of Urology. 1997;157(3):1059–1063. [PubMed: 9072543]
24. Thamilselvan S, Khan SR, Menon M. Oxalate and calcium oxalate mediated free radical toxicity in renal epithelial cells: Effect of antioxidants. Urological Research. 2003;31(1):3–9. [PubMed: 12624656]
25. Yoshida K. The correlation between tissue injury and calcium oxalate crystal production in rat's lung with experimental Aspergillus niger infection. The Journal of the Japanese Association for Infectious Diseases. 1998;72(6):621–630. [PubMed: 9695473]

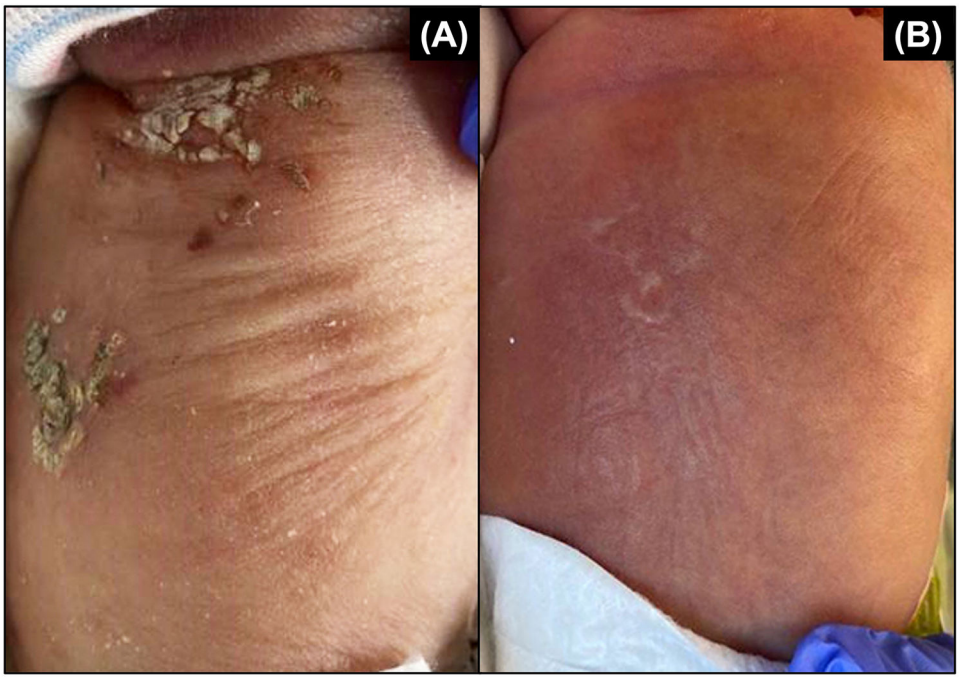

Figure 1.
(A) Initial dermatological examination showing multiple irregularly shaped plaques with yellow and grey hemorrhagic crust on the mid and upper back; (B) Resolved back lesions 40 days after completing treatment.

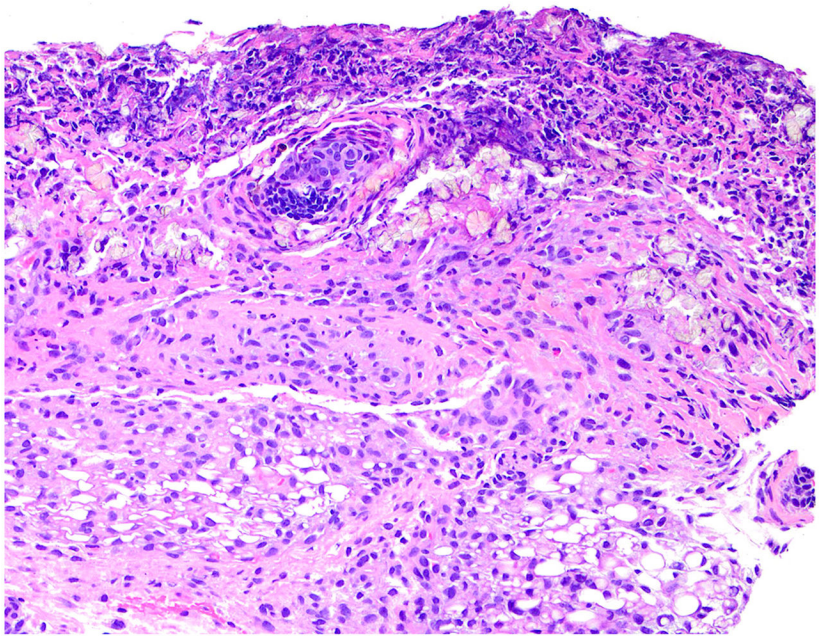

Figure 2.
Histopathology of back lesion showing ulcerated skin with superficial radially-arranged, needle-shaped crystals and inflammatory infiltrates (hematoxylin and eosin stain; 100x magnification).

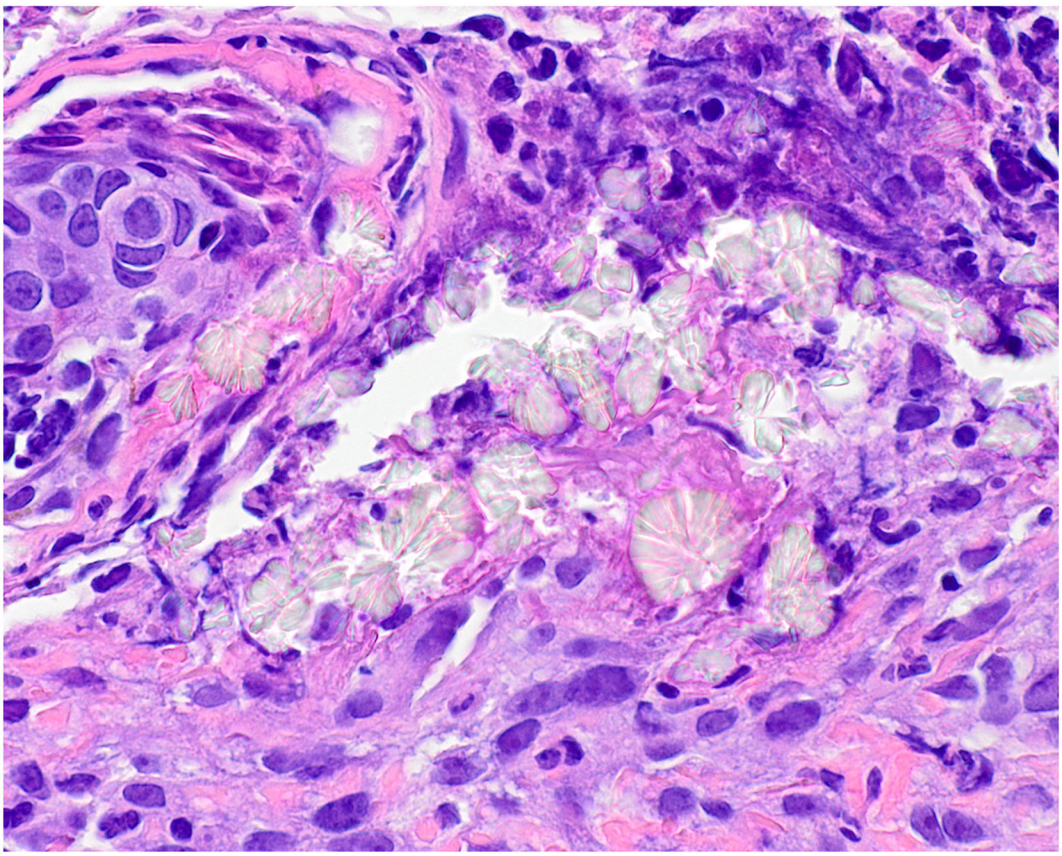

Figure 3.
Histopathology of radially-arranged, needle-shaped crystals identified as calcium oxalate crystals (hematoxylin and eosin stain; 400x magnification).

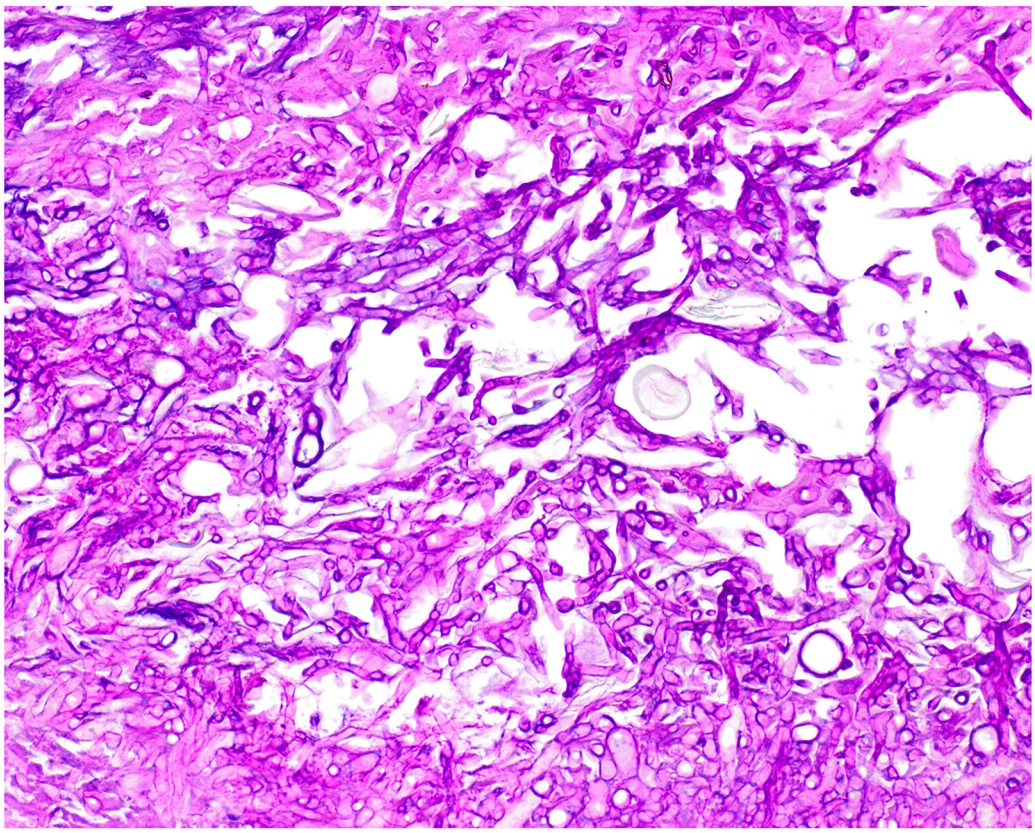

Figure 4.
Histopathology of superficial crust showing numerous PAS-D positive septate hyphae with acute angle branching (PAS-D stain; 400x magnification).