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J Case Rep Images Pathol 2023;9(1):1–6.
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CASE REPORT PEER REVIEWED | OPEN ACCESS

Idiopathic calcinosis cutis with unusual histomorphology and negative von Kossa stain: A diagnostic pitfall

Trent Irwin, Mugahed Hamza, Evan George, Ata S Moshiri

ABSTRACT

Introduction: Calcinosis cutis is characterized by basophilic crystalline or amorphous calcium within the dermis/subcutis. Calcinosis cutis has many different clinical subtypes and associated etiologies that may lead clinicians to consider this diagnosis. Von Kossa and/or Alizarin red special stains may be used by pathologists to highlight deposition of insoluble calcium salts, especially in histologically ambiguous or subtle cases.

Case Report: We report the case of a 27-year-old male who presented with an inferior right buttock mass clinically diagnosed as epidermal inclusion cyst(s). Gross pathology revealed a gray-white pasty substance within a cyst-like structure. Histopathologic examination demonstrated pools of amorphous blue-gray material with rare deposits of admixed coarse calcifications surrounded by foreign-body giant cells. No cyst wall was seen in the specimen. Special stains, including von Kossa, were initially negative. Following additional review, it was discovered that surface decalcifying solution had been applied to the paraffin block in the histology lab prior to microtome sectioning. Hypothesizing that this could be the cause of the unusual morphology, the paraffin block was reprocessed and subsequent H&E-stained sections displayed characteristic basophilic calcium deposits, which were correspondingly positive by von Kossa stain.

Conclusion: The histopathologic diagnosis of calcinosis cutis is apparent by H&E in most cases, though von Kossa and/or Alizarin red special stains can be used to aid the pathologist. Given the unusual histomorphology following surface decalcification and initial lack of von Kossa stain prior to reprocessing, this report serves to make pathologists aware of this potential diagnostic pitfall.

Keywords: Calcinosis cutis, Histomorphology, von Kossa

How to cite this article

Irwin T, Hamza M, George E, Moshiri AS. Idiopathic calcinosis cutis with unusual histomorphology and negative von Kossa stain: A diagnostic pitfall. J Case Rep Images Pathol 2023;9(1):1–6.

Article ID: 100067Z11TI2023

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doi: 10.5348/100067Z11TI2023CR

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Received: 06 December 2022
Accepted: 02 February 2023
Published: 22 February 2023

INTRODUCTION

Calcinosis cutis (CC) is caused by the deposition of insoluble calcium salts within skin and subcutaneous tissue [1]. There are five subtypes of CC: dystrophic, metastatic, idiopathic, iatrogenic, and calciphylaxis [1, 2]. The histomorphology of CC is typically characterized by fine granules or nodules of basophilic crystalline or amorphous calcium within the dermis/subcutis [3]. If performed, special staining with von Kossa and/or Alizarin red should be positive [1]. We report a case of CC, clinically diagnosed as an epidermal inclusion cyst (EIC), which initially had ambiguous histomorphology consisting of pools of pale blue-gray material by H&E stain which were negative by von Kossa stain. Upon additional review, these findings were discovered to be the result of surface decalcification of the paraffin

block, something confirmed after reprocessing of the tissue.

CASE REPORT

A 27-year-old male with no significant past medical history presented to the surgery clinic and complained of an inferior right buttock mass which had been present for at least eight years. The patient had been referred by dermatology to have the mass surgically excised in 2013 but was lost to follow up. In the years that followed, the patient described increasing discomfort while sitting, as well as multiple sporadic episodes of thick, foul-smelling drainage from the mass.

Physical exam revealed a subcutaneous mass (3×1 cm) with induration, minimal tenderness, mild erythema, and no evidence of drainage or fluctuance. The clinician noted that the mass had two adjacent heads and was felt to be consistent with EIC. The physical exam was otherwise unremarkable. The most recent laboratory findings, including calcium (though measured in 2015) were unremarkable. The patient had no systemic findings to suggest connective tissue disease or metabolic disorder.

Surgical excision demonstrated two hard, pea-sized masses underlying the skin with subsequent gross pathology revealing a gray-white pasty substance within a cyst-like structure. The specimen was entirely submitted without decalcification. Histologic examination revealed multiple pools of blue-gray, acellular material within the dermis with foreign body giant cell reaction and fibrosis. Occasional focal and minute basophilic calcifications were noted on H&E (Figure 1).

Given the unusual homogenous morphology, a differential diagnosis was considered that included calcinosis cutis/tumoral calcinosis, old cyst contents, exogenous filler material, or injection/traumatic implantation to the site. Epidermal inclusion cyst or other cystic processes were not favored due to lack of an identifiable cyst wall or keratin. The absence of staining by von Kossa or Alcian blue (controls appropriately positive) also argued against calcinosis or exogenous filler material, respectively (Figure 1). Polarizable material was not present. The patient did not have a clinical history of injections or known trauma. Immunohistochemical studies were performed due to rare cells within the amorphous material. S100 (negative), AE1/AE3 (negative), and CD163 (positive) confirmed the histologic impression of reactive macrophages. The final diagnosis was descriptive of an amorphous material in the dermis with surrounding foreign body giant cell reaction and the pathology report proposed the above differential diagnosis.

Upon subsequent review of the case, it was determined that the overall histomorphologic architecture with associated focal, small calcifications likely did represent an unusual presentation of CC. Additional case tracking in the electronic health record revealed that although decalcification didn't occur at grossing, processing issues in the histology lab led to the embedded tissue blocks being placed in a medium-strength surface decalcification solution for ≈5–10 minutes prior to sectioning. This additional information prompted our team to reprocess the block by melting the paraffin, flipping the tissue 180° to display the surface which had not been previously exposed to surface decalcification and re-embedding the block. Repeat H&E stain showed nodular collections of basophilic material characteristic of calcifications, which were also strongly positive by von Kossa stain, consistent with a diagnosis of calcinosis cutis (Figure 2). The patient had no complications at follow-up.

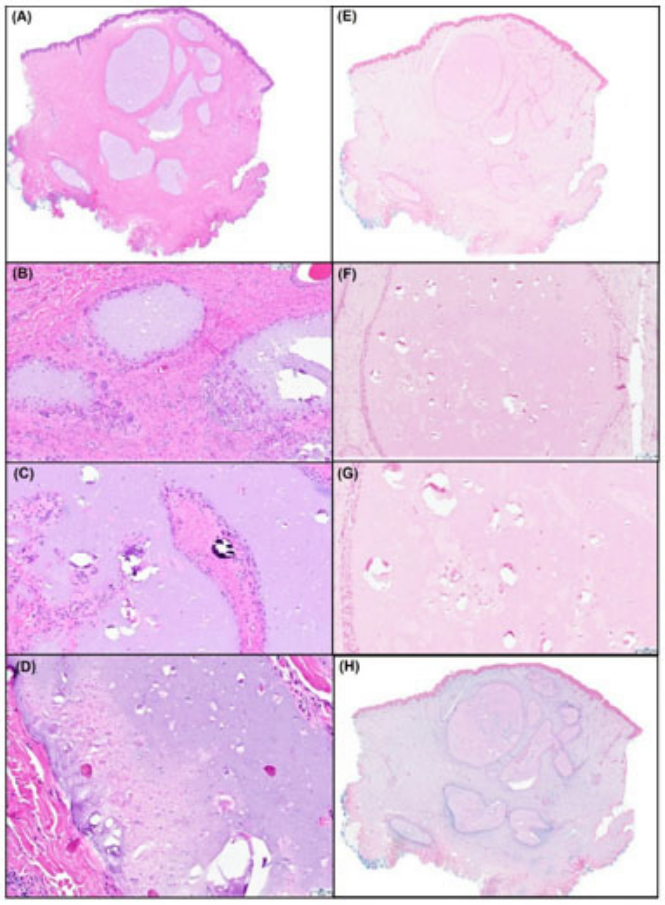

Figure 1: (A) Histologic examination revealed multiple pools of amorphous, blue-gray material within the superficial to deep dermis at low power, hematoxylin-eosin, 1×. (B) Scattered regions demonstrated granulomatous reaction with multinucleated giant cells and fibrosis, hematoxylin-eosin, 10×. (C and D) Occasional focal, minute basophilic calcifications were noted, hematoxylin-eosin, 10× (C); hematoxylin-eosin, 20× (D). (E–H) Areas of interest were negative by von Kossa [(E) 1×; (F) 4×; (G) 10×)] and negative by Alcian blue [(H), 1×)].

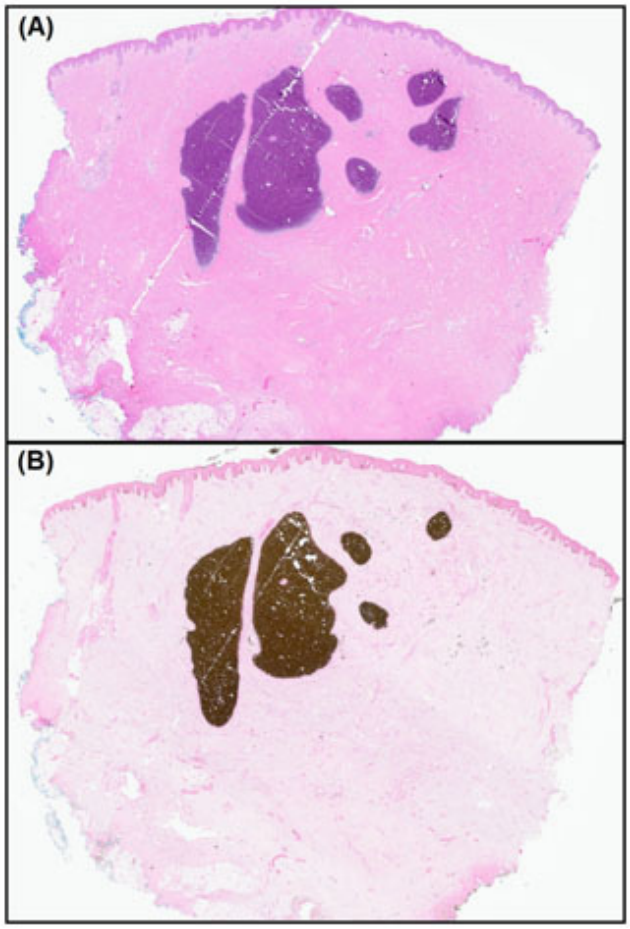

Figure 2: (A) The reprocessed block displayed characteristic basophilic calcifications (hematoxylin-eosin, 1×) and (B) positive von Kossa stain (1×), as typically seen in calcinosis cutis.

DISCUSSION

Calcinosis cutis was first described by Virchow in 1855 and was later subclassified into multiple categories [1, 4]. Dystrophic CC is the most common form and is caused by local collagenous, elastic, or subcutaneous tissue damage. Dystrophic CC occurs in the setting of normal serum calcium and phosphate levels. Metastatic CC is a systemic disorder caused by abnormal calcium and/or phosphate metabolism, leading to elevated serum levels that induce calcium precipitation in the skin. Idiopathic CC is the second most common form and is a diagnosis of exclusion made when clear tissue damage or metabolic disorder is not identified. Iatrogenic CC is caused by any medical intervention which leads to calcium deposition. Calciphylaxis, the most dramatic subtype of CC, is defined as the calcification of small to medium-sized vessels in the deep dermis and subcutis, possibly leading to cutaneous ulceration and necrosis. Calciphylaxis is associated with a particularly grim prognosis [1]. A list of diagnoses and pathologic processes associated with these CC subtypes is detailed elsewhere (Table 1) [1, 2, 4–21]. Though our patient did not have autoimmune titers or recent serum

Table 1: Calcinosis cutis subtypes and a list of their associated diagnoses/processes

Calcinosis cutis subtypes	Associated diagnoses/processes
Dystrophic	Connective tissue diseases [1, 2, 5–9] - Systemic sclerosis - Scleroderma - Systemic lupus erythematosus (SLE) - Dermatomyositis - Mixed connective tissue disease Inherited disorders [1] - Pseudoxanthoma elasticum - Werner syndrome - Ehlers-Danlos syndrome Neoplasms [1, 4, 10–12] - Pilomatricoma - Pilar cyst - Basal cell carcinoma - Desmoplastic trichoepithelioma Infections [1, 13, 14] - Cysticercosis - Onchocerciasis - Histoplasmosis - Cryptococcus - Chikungunya Trauma [1, 4, 15–17] - Fractures - Burn scar - Heel stick Other [1, 18, 19] - Porphyria cutanea tarda - Chronic graft versus host disease (GVHD) - Pancreatic and lupus panniculitis - Acne vulgaris
Metastatic	Milk-alkali syndrome [1, 4] Hypervitaminosis D [1, 4] Sarcoidosis [2, 4] Hyperparathyroidism [1] Albright hereditary osteodystrophy [4] Epithelial malignancies [2, 4] Hematologic malignancies [20, 21]
Idiopathic	Diagnosis of exclusion—three forms include: [1, 2, 4, 10] - Tumoral calcinosis - Subepidermal calcified nodule - Scrotal calcinosis
Iatrogenic	Medical therapies including: [1, 16] - Solid organ transplants - Calcium chloride electrode paste - IV calcium gluconate - IV para-aminosalicylic acid - Vaccination
Calciphylaxis	End-stage renal disease (ESRD) [1, 2] Disturbances of calcium and phosphate metabolism

calcium or phosphate levels, he also did not have clinical findings which would suggest a CTD or other systemic process. He additionally did not have a history of known trauma or medical therapies/injections to the area. Given these findings, the patient was best classified as having idiopathic CC, though additional clinical and laboratory workup could have been considered.

The histopathologic differential diagnosis of CC may include gout, oxalosis, and osteoma/chondroma cutis [3]. The lack of polarization or osteocytes/chondrocytes made these diagnoses unlikely in our patient. Given the initial gray-blue, amorphous nature of the specimen, relative lack of basophilic calcifications, and negative von Kossa, diagnostic consideration had been given to an exogenous dermal filler. However, review of the literature did not describe a dermal filler that could cause the morphologic findings seen in our case prior to reprocessing of the block [22–24]. In addition, the negative clinical history of a dermal filler or injection of other exogenous material in the context of a negative Alcian blue stain also made this diagnosis unlikely.

The histologic features which were seen in this report prior to block reprocessing were unusual. Cases of CC previously reported in the literature have shown more eosinophilic and/or homogenous CC with a lack of or very little basophilic calcifications, but we were unable to find a reported case which displayed the same unique initial morphology as seen in this patient [25, 26]. Some of the literature describes proposed inactive or early stages of tumoral calcinosis, which may have an amorphous appearance [25, 26]. However, it had seemed unlikely that the patient in our case had an early stage of calcification given the presence of the mass for many years. The originally negative von Kossa was also especially perplexing at first, and we were unable to find prior literature describing diagnostic pitfalls using von Kossa in this setting or of false negative staining in general. The use of medium-strength surface decalcification (dilute formic acid and hydrochloric acid, Easy*Cut Decal Solution) on the tissue block in this case, even after only a limited amount of time in solution, almost completely demineralized the present calcifications. This drastically altered the histomorphology and led to a completely negative von Kossa stain, representing a source of diagnostic pitfall. The definitive diagnosis of calcinosis cutis was made only after melting and re-embedding the previously unexposed/non-decalcified side of the paraffin block. The patient had no relevant clinical issues upon follow-up.

CONCLUSION

This case serves to increase awareness of this potential diagnostic pitfall in CC due to an unusual histologic presentation in the context of a negative von Kossa stain following surface decalcification, while also highlighting some of the differential diagnoses associated with the various subtypes of CC.

REFERENCES

1. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: Part I. Diagnostic pathway. J Am Acad Dermatol 2011;65(1):1–12.
2. Jiménez-Gallo D, Ossorio-García L, Linares-Barrios M. Calcinosis cutis and calciphylaxis. Actas Dermosifiliogr 2015;106(10):785–94.
3. Elston D, Elston CA. Calcinosis cutis. 2021. [Available at: https://app.expertpath.com/document/calcinosis-cutis/36b9507a-86cc-4787-bf24-2bc7226cbfa2?searchTerm=calcinosis%20cutis]
4. Whitlock R, Chiu Y. Characterizing calcinosis cutis in a pediatric population. Pediatr Dermatol 2020;37(2):317–9.
5. Gutierrez A Jr, Wetter DA. Calcinosis cutis in autoimmune connective tissue diseases. Dermatol Ther 2012;25(2):195–206.
6. Balin SJ, Wetter DA, Andersen LK, Davis MDP. Calcinosis cutis occurring in association with autoimmune connective tissue disease: The Mayo Clinic experience with 78 patients, 1996–2009. Arch Dermatol 2012;148(4):455–62.
7. Valenzuela A, Song P, Chung L. Calcinosis in scleroderma. Curr Opin Rheumatol 2018;30(6):554–61.
8. Chattopadhyay A, Mishra D, Sharma SK. Calcinosis cutis at an unusual location. J Clin Rheumatol 2020;26(6):e200.
9. SaterenZoller E, Rizzo M, Harris A. Understanding calcinosis cutis. JAAPA 2020;33(11):25–8.
10. Bernhisel AA, Zaugg BE, Mamalis N, Dutton JJ, Patel BCK. An unusual case of idiopathic calcinosis of the eyelid. Orbit 2019;38(6):500–2.
11. Ito A, Sakamoto F, Ito M. Dystrophic scrotal calcinosis originating from benign eccrine epithelial cysts. Br J Dermatol 2001;144(1):146–50.
12. Forouzan P, Calame A, Uebelhoer NS, Cohen PR. Basal cell carcinoma with calcification: Case report of calcifying basal cell carcinoma and review of calcinosis cutis associated with basal cell carcinoma. Cureus 2021;13(1):e12721.
13. Le C, Bedocs PM. Calcinosis Cutis. 2022 Jul 12. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
14. Srinivas SM, Pradeep GCM. Congenital chikungunya infection presenting with extensive dystrophic calcinosis cutis. Indian J Dermatol Venereol Leprol 2020;86(6):693–6.
15. Rosmaninho A, Carvalho S, Lobo I. Photoletter to the editor: Calcinosis cutis in a burn scar. J Dermatol Case Rep 2015;9(4):120–1.
16. Rumancik BE, Rahnama-Moghadam S. Severe iatrogenic calcinosis cutis from extravasated calcium gluconate. Cureus 2020;12(8):e9712.
17. Larralde M, Giachetti A, Cáceres MR, Rodríguez M, Casas J. Calcinosis cutis following trauma. Pediatr Dermatol 2005;22(3):227–9.

18. Saardi KM, Rosenstein RK, Anadkat MJ, et al. Calcinosis cutis in the setting of chronic skin graft-versus-host disease. JAMA Dermatol 2020;156(7):814–7.
19. Sahu SK, Gupta N, Vohra S. Calcinosis cutis secondary to facial acne vulgaris: A rare complication. Indian Dermatol Online J 2015;6(Suppl 1):S37–9.
20. Dennin MH, Dulmage BO, Yazdan P, Keimig E. Metastatic calcinosis cutis in a patient with Hodgkin's lymphoma. Dermatol Online J 2018;24(11):13030/qt7z73b3kk.
21. Altman I, Lee IH, Burns MR, Rondelli D, Ennis WJ. Calcinosis cutis presenting in the context of long-term therapy for chronic myeloid leukemia: A case report and review of the literature. Wounds 2015;27(2):20–5.
22. Mercer SE, Kleinerman R, Goldenberg G, Emanuel PO. Histopathologic identification of dermal filler agents. J Drugs Dermatol 2010;9(9):1072–8.
23. Molina-Ruiz AM, Requena L. Foreign body granulomas. Dermatol Clin 2015;33(3):497–523.
24. El-Khalawany M, Fawzy S, Saied A, Al Said M, Amer A, Eassa B. Dermal filler complications: A clinicopathologic study with a spectrum of histologic reaction patterns. Ann Diagn Pathol 2015;19(1):10–5.
25. Slavin RE, Wen J, Barmada A. Tumoral calcinosis—A pathogenetic overview: A histological and ultrastructural study with a report of two new cases, one in infancy. Int J Surg Pathol 2012;20(5):462–73.
26. Mohamed S, Jong-Hun J, Weon-Yoo K. Tumoral calcinosis of the foot with unusual presentation in an 11-year-old boy: A case report and review of literature. J Postgrad Med 2007;53(4):247–9.

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Author Contributions

Trent Irwin – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mugahed Hamza – Conception of the work, Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Evan George – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ata S Moshiri – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.