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Author
Mahmood, Muhammad N

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Calciphylaxis: how specific are the pathological features: avoiding false-positives and false-negatives

Author: Muhammad N Mahmood MD

Affiliation: Department of Laboratory Medicine & Pathology, University of Alberta Hospital, Edmonton, Alberta, Canada

Corresponding Author: Muhammad N Mahmood MD, 5B4.55 WMC, 8440-112 Street, Laboratory Medicine & Pathology, University of Alberta Hospital, Edmonton, AB T6G2B7, Canada, Tel: 780-407-2145, Fax: 780-407-3009, Email: noshpath97@gmail.com

Abstract

Calciphylaxis is considered a critical inflammatory dermatosis with potentially devastating clinical consequences. Skin biopsies are expedited for evaluation and are often considered as a gold standard for diagnostic confirmation and exclusion of other conditions. The key histopathological features include a combination of vascular and extra-vascular calcifications, intravascular microthrombi, and changes related to resulting ischemia. The pathological diagnosis of calciphylaxis is not always a straightforward process as it can be influenced by a number of factors. The specificity of pathological diagnosis of calciphylaxis has been questioned and a systematic approach with multidisciplinary collaboration is required to avoid potential errors.

Keywords: calciphylaxis, critical dermatosis, dermatopathology, histopathology, specificity

Introduction

Calciphylaxis is an uncommon, albeit potentially devastating, multifactorial cutaneous vascular condition which continues to be a diagnostic and therapeutic challenge [1,2]. Less commonly, it is known by more descriptive and explanatory appellations which consider pathological changes, such as calcific uremic arteriolopathy and uremic small artery disease with medial wall calcifications and intimal hyperplasia [2,3]. Over the years, it continues to be a condition with high morbidity and mortality, manifesting in patients with chronic kidney disease (CKD), especially end-stage renal disease patients on hemodialysis (uremic calciphylaxis), [4]. Less commonly, it is also described in patients with normal renal function or in early stages of kidney disease (non-uremic calciphylaxis), [5]. When multi-organ ischemic involvement ensues, the term systemic calciphylaxis is employed [6].

Historically, the term calciphylaxis was first used and introduced by Selye et al. in 1961, when they induced subcutaneous calcifications in rats as an adaptive reaction [7]. After the animal model description of calciphylaxis, a comparable phenomenon of widespread calcifications in patients with CKD was described as its human counterpart [8-10]. The link between the originally described experimental model and the expression of this condition in humans is debated; however, the term calciphylaxis remains to be the preferred and ubiquitous designation.

Discussion

The pathogenetic mechanisms behind calciphylaxis are intricate, multifaceted, and elusive. It remains to be determined if it is strictly a distinct disorder or merely occlusive vasculopathy, related to a variety of triggers, with a worse outcome in a high-risk population. Simply, it can be regarded as a two-phase process of calcific thrombogenic microangiopathy. In the first phase, medial calcifications and intimal proliferation of arterioles and capillaries occurs primarily in the subcutaneous fat. In the second phase, thrombotic occlusion of

Table 1. *McCarthy et al. criteria for diagnosis of calciphylaxis [33].*

	Clinical criteria	Microscopic criteria
Major	-Necrotic cutaneous ulcers (over indurated plaque) -Indurated plaque without ulcer in adipose rich tissue (abdominal pannus, breasts, buttocks, and thighs)	-Medial calcifications and intimal fibroplasia of pannicular arterioles with cutaneous necrosis
Minor	-Livedo racemosa -Hemorrhagic plaques -Hemorrhagic bullae	-Extravascular calcium deposition -Thrombosis of pannicular or dermal arterioles

vessels ensues, leading to ischemic necrosis and painful ulcers [11,12]. These non-healing ulcers frequently get secondarily infected and progress to systemic infections, sepsis, and death in 45-80% of patients within one year [13]. Imbalanced calcium-phosphorous metabolism in CKD patients, pro-calcification treatments, and hyperparathyroidism act as potential contributors to the primary step of vascular calcifications. For the succeeding step of thrombotic occlusion, various hypercoagulable states likely play pivotal roles as triggering factors [11,12,14]. Protein C and S deficiency and warfarin use have been especially linked as exacerbation factors [15-17].

Skin biopsy and histopathological signature

Clinicopathological correlation is essential for accurate diagnosis and prompt recognition. Skin biopsy for pathological analysis is a crucial tool, often considered as the gold standard to confirm the diagnosis and exclude other conditions [1,18]. Appropriately performed biopsy plays an imperative part in completing the diagnostic puzzle, especially in the detection of early-stage non-ulcerated lesions, even though the risk of acquiring a non-healing ulceration at the biopsy site is a valid and legitimate concern [19]. As ulcerated lesions are related to poorer outcome and higher mortality, early identification and intervention may well avert progression. Sampling of subcutaneous fat is of utmost importance. An excisional biopsy or a 6-8mm deep punch biopsy from the verge of the eschar or indurated margin is advised. A telescoping smaller punch biopsy at the base of the larger punch can also be considered [1,20].

A combination of finely stippled and/or chunky medial and endoluminal calcifications in small-to-medium-sized arterioles and capillaries in the subcutaneous fat and/or lower dermis, fibrointimal hyperplasia of involved vessels with resulting luminal narrowing, extravascular calcifications (particularly peri-eccrine calcifications), intravascular thrombi and ensuing changes related to cutaneous ischemia are considered as the core histopathological signatures of this condition [21-23]. Diffuse dermal angiomatosis and pseudoxanthoma elasticum-like changes have also been reported [24,25]. The occurrence of intravascular thrombi has been linked with cutaneous pain severity [26]. Pathological features of calciphylaxis are indistinguishable in CKD and non-CKD patients [21]. Use of special stain to enhance detection of microcalcifications (von Kossa or Alizarin red) is recommended and regularly utilized [22]. Special stains for microorganisms and tissue cultures from the wound are valuable in evaluating for superimposed infections. Mere occurrence of vascular calcifications should not be considered diagnostic as other conditions can also demonstrate their presence. For example, Monckeberg medial calcific sclerosis can show medial arterial calcifications. However, they tend to be coarse-dystrophic in nature, generally affect larger arteries, and commonly lack fibrointimal hyperplasia and occlusive thrombi. Also, there are clinical differences as this condition is generally incidentally identified and is clinically asymptomatic [27].

Lack of histopathological specificity and false-positives

Owing to the high morbidity and mortality coupled with this disorder, it is considered as a critical inflammatory dermatosis with biopsies typically expedited for evaluation [28]. The opinion hinges on finding vascular and extra-vascular calcifications with fibrointimal hyperplasia and occlusion by thrombi [22,23]. However, the specificity of these pathological features has been questioned [29-31].

Ellis et al. compared the pathological findings in skin biopsies performed for suspicion of calciphylaxis versus skin samples obtained from healthy margins of amputations in patients with CKD (but lacking any known clinical evidence of calciphylaxis), [29]. Their results reveal that each of the microscopic changes described for calciphylaxis can occur in CKD patients lacking any clinical evidence of this disorder. They conclude that none of these findings can be deemed diagnostic in isolation. However, they do highlight that the simultaneous combination of small artery medial calcifications and thrombosis are more common in biopsies suspected for calciphylaxis. Their findings underscore the two-step premise that calciphylaxis results from acute infarctive changes in a setting of chronic low-grade ischemia in calcified vessels; however, the specificity of individual features is questioned in this retrospective analysis.

In a more recent investigation, Chaudet et al. similarly report that the pathological features of calciphylaxis are non-specific as they can be encountered in patients lacking any known proof of this disorder [31]. In their single-institutional retrospective study, they assess viable and healthy marginal skin tissue from above the knee amputation specimens from 70 patients. The pathological features attributed to calciphylaxis are compared between CKD and non-CKD cohorts of patients. None of their patients had any clinical evidence of calciphylaxis (at least one-year follow-up). They observe that 40% of all cases had vascular calcifications of capillaries or small-to-medium arterioles. Finely stippled capillary calcifications were more prevalent in patients with CKD than those without CKD (26.1% versus 8.5%). Intravascular thrombosis was also identified in 8.7% of patients with CKD; however, the non-CKD cohort did not demonstrate this feature. Moreover, extravascular calcifications were found to be more prevalent in patients who were treated with warfarin. They concluded that both vascular calcifications and thrombosis were more common in patients with CKD, even without any known evidence of calciphylaxis.

The lack of specificity illustrated by these analyses is concerning as it can lead to a false positive pathological diagnosis of calciphylaxis, particularly in patients with history of CKD. Chronic kidney disease patients, specifically those on hemodialysis, are regularly treated at tertiary care centers. As the probability of calciphylaxis is high in this cohort, any cutaneous ulceration is generally handled with suspicion, often eventuating in a biopsy. 'Rule-out calciphylaxis' is sometimes stated on pathology requisitions mainly due to the overall clinical situation, without first precisely determining the clinical parameters which distinguish this disorder from other cutaneous ulcerating diseases. If a subset of CKD patients can display pathological alterations traditionally linked with calciphylaxis (without truly suffering from calciphylaxis), the combination of these microscopic changes and the bias related to the scenario can lead to a potential diagnostic error.

Suboptimal biopsy samples and false-negatives

These investigations raise the concern of false-positive diagnosis of calciphylaxis; conversely, false-negative pathological diagnosis cannot be overlooked as well. Insufficient or inadequate samples for evaluation is a foremost concern, with a report by Williams et al. that determined that 29% of samples submitted to exclude calciphylaxis were inadequate [32]. The reasons for this shortfall were absence of subcutaneous adipose tissue, tissue decalcification by the laboratory, and completely necrotic tissue samples. Interestingly, they also found significant correlation between both initial clinician being a dermatologist and specimen initially sent to a private laboratory with inadequacy of biopsies. Inadequate sampling, lack of dermatopathology fellowship training, and failure to employ special stains for calcium were detected as elements related to false-negative pathological diagnosis. A larger prospective analysis will be ideal to validate and authenticate these outcomes. However, this retrospective inquiry does emphasize some vital issues which can definitely lead to a missed diagnosis. A deep biopsy incorporating ample subcutaneous adipose tissue, interpreted by a

fellowship-trained dermatopathologist can reduce this diagnostic error.

Interdisciplinary collaboration to avoid errors

The correct diagnosis of calciphylaxis can be sometimes tricky even for a dermatopathologist, and an approach to avoid a potential diagnostic error is necessary. Calciphylaxis is a clinicopathological diagnosis and optimum chance for correct diagnosis necessitates clinical evaluation by an experienced clinician with a good understanding of this disorder. Collaboration of a calciphylaxis multidisciplinary team (comprising dermatology, nephrology, dermatopathology, surgery, nutrition, and pain management specialties) is ideal for the best diagnosis and treatment [2].

McCarthy et al. presented an excellent clinicopathological classification plan in their investigation to identify patients with calciphylaxis [33]. The patients are ranked as negative, possible,

Table 2. *Calciphylaxis and its differential diagnosis.*

	Clinical features	Microscopic features
Calciphylaxis	-Necrotic painful ulcers-eschars -ARA, CKD patients	-Medial calcifications, intimal fibroplasia, necrosis -IVT, extravascular calcifications -von Kossa or Alizarin red+
Warfarin necrosis	-First 10 days of therapy -ARA, female, obese -Improvement on WF cessation -Calciphylaxis triggered by WF therapy: WF-exposure of prolonged duration	-IVT -Cutaneous necrosis, hemorrhage with blood-filled bullae
Purpura fulminans	-Geographic necrosis, symmetrical -Widespread, starts acral progresses proximally, rapid progression, children -DIC or septic shock	-IVT, sparse inflammatory infiltrate -Cutaneous necrosis, hemorrhage with blood-filled bullae
Cholesterol embolization	-RP, necrotic ulcerations-gangrene -Acral, elderly male, severe atherosclerotic disease, post-catheterization, prolonged anticoagulation, multisystem involvement	-OVL with elongated, biconvex, needle-shaped cholesterol clefts -Clefts represent crystals dissolved by xylene- and alcohol-based tissue processing
Oxalate embolization	-RP, necrotic ulcerations-gangrene -Acral, primary and secondary oxalosis, nephrolithiasis, CRF	-OVL with birefringent, polarizable, yellowish-brown, radially arranged, crystalline material, media of arteries involved
Heparin necrosis	-Site of heparin injection (5-14 days after treatment initiation) -HIT syndrome	-OVL with platelet plugs ('white clots') -CD61+
Cryoglobulinemias	-Monoclonal CG (type-I) -Digits, ear, nose, in winter -Meltzer's triad: purpura, arthralgia, weakness	-Monoclonal CG (type I): OVL with eosinophilic homogenous CRYO -PAS+ diastase resistant, IgG DIF+ luminal deposits -Mixed CG: LCV
Ecthyma gangrenosum	-Black necrotic center, ecchymotic halo, neutropenic patients - Usually Pseudomonas aeruginosa	-OVL with granular basophilic material (representing microorganisms)
Polyarteritis nodosa	-Localized cutaneous: tender papules and plaques, RP, ulcerations, lower extremities -Systemic: multiple organ systems	-Microscopic changes similar in cutaneous and systemic forms -Vasculitis of small to medium-sized arteries in deep dermis and subcutis
Peripheral vascular disease	-Weak peripheral pulses, distal extremity-acral punched out dry ulcers -Abnormal ABI, claudication	-Atherosclerotic intimal calcifications, eccentric lumen deforming and labile

ABI, ankle-brachial index; ARA, adipose rich areas; CG, cryoglobulinemia; CKD, chronic kidney disease; CRF, chronic renal failure; CRYO, cryoprecipitate; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; IVT, intravascular thrombi; LCV, leukocytoclastic vasculitis; OVL, occluded vascular lumina; PAS, periodic acid-Schiff; RP, retiform purpura; WF, warfarin

probable, and definite calciphylaxis groupings based on the presence and number of major and minor clinical and histopathological criteria (**Table 1**). Utilizing both clinical and pathological criteria ensures a high probability of calciphylaxis in the selected patients. The differential diagnosis and mimics of calciphylaxis can include a variety of conditions including a gamut of occlusive (non-vasculitic) vasculopathies, vasculitides, and peripheral vascular disease (**Table 2**), [1,34-36]. The vascular and extravascular calcifications comprising the major and minor pathological criteria are historically considered as the hallmark features differentiating calciphylaxis from other entities. Intravascular thrombi, one of the minor pathological criteria, on its own is less helpful as it can be seen in a number of other occlusive vasculopathies. However, the combination of calcifications and thrombosis of small vessels does result in improved sensitivity and specificity for the diagnosis of calciphylaxis [29,34]. A classification plan such as this is not only suitable for forming inclusion benchmarks for a study, but can also be utilized for diagnosis of this condition in routine clinical practice.

A similar clinicopathological scoring system can be designed by interdisciplinary collaborators at various tertiary care centers. Use of possible or probable (or an analogous term) for calciphylaxis in pathology reports, rather than outright unequivocal diagnosis based on histopathology alone, can be a prudent approach in challenging cases. For proper communication, a short statement in the report which emphasizes a certain degree of uncertainty linked with this diagnosis can aid in recognizing the significance of clinical context in this setting. Where experienced dermatology services are not accessible, availability of clinical images to dermatopathologists can also facilitate the diagnostic process [37]. In addition, if the biopsy is inadequate, a dermatopathologist should not hesitate to report that detail so that if clinically warranted, an additional biopsy can be performed.

Conclusion

In sum, the histopathological characteristics attributed to calciphylaxis are not entirely specific. Calciphylaxis requires multidisciplinary teamwork and collaboration for diagnosis and treatment. In view of the relative lack of pathological specificity, an argument for limiting the role of biopsy can be plausible. However, if systematically performed in the correct clinical context, the tissue biopsy is a valuable diagnostic tool. With experience, most dermatopathologists recognize these factors and dilemmas. However, in-training or recently trained dermatopathologists and those pathologists who do not encounter calciphylaxis regularly should understand these concerns to prevent mistakes and resulting clinical frustration.

Potential conflicts of interest

The author declares no conflicts of interest.

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