Review Article

Calciphylaxis and its diagnosis: A review

Deepak Baby[1], Meenakshi Upadhyay[2], M. Derick Joseph[1], Swati Joshi Asopa[3], Basanta Kumar Choudhury[4], Jagadish Prasad Rajguru[5], Shivangi Gupta[6]

[1]Department of Conservative Dentistry and Endodontics, P.S.M Dental College and Research Centre, Akkikavu, Thrissur, Kerala, [2]Department of Pediatric and Preventive Dentistry, Saraswati Dental College, Lucknow, Uttar Pradesh, [3]Department of Prosthodontics, Rajasthan Dental College and Hospital, Jaipur, Rajasthan, [4]Department of Oral Medicine and Radiology, Institute of Dental Sciences, Siksha 'O' Anusandhan (Deemed to be University), [5]Department of Oral and Maxillofacial Pathology, Hi-Tech Dental College and Hospital, Bhubaneswar, Odisha, [6]Department of Periodontics, Private Practitioner, Chandigarh, India

Abstract

Calciphylaxis also known as Calcific uremic arteriolopathy (CUA), is a rare fatal complication usually associated with end-stage renal disease (ESRD). It is characterized by skin ulceration and necrosis leading to significant pain. The disease calciphylaxis is pathological state resulting in accumulation of calcium content in medial wall of small blood vessels along with the fibrotic changes in intima. The aetiopathogenesis of this disease, small vessel vasculopathy, remains complicated, and unclear. It is believed that development of calciphylaxis depends on medial calcification, intimal fibrosis of arterioles and thrombotic occlusion. The disease is rare, life-threatening medical condition that occurs mostly in population with kidney disease or in patients on dialysis. Skin biopsy and radiographic features are helpful in the diagnosis of calciphylaxis, but negative results do not necessarily exclude the diagnosis. This article highlights steps undertaking in the diagnosis of calciphylaxis.

Keywords: Calciphylaxis, calcium, small blood vessels

Introduction

Calciphylaxis is characterized by intense deposition of calcium in small blood vessels, skin, and other organs that develops as a result of secondary hyperparathyroidism, and is associated with end-stage renal disease (ESRD).[1] Bryant and White[2] in 1898 first described the disease later in 1962 Hans Selye coined the term "calciphylaxus".[3,4] The disease is rare but devastating, increasing in dialysis population[5] and its aetiology is still unmasked that is challenging demonstrates a challenge for different specialities. Even if diagnosed in early stages, the mortality rate remains exceptionally high and the success in healing is low.[6] Mortality rates are estimated at 60-80%.[7] Furthermore, the disease is characterized by skin ulcerations that undergo necrosis leading to intense pain and can be localized on any part of the skin.[6] It is manifested in patients on renal replacement therapy or with low glomerular filtration, whose alteration of phosphorus and calcium metabolism seems to represent the main cause of this pathology.[8] Wounds are sometimes secondarily infected and may even cause death in most of the patients. The disease can be seen even in absence of renal failure as the kidney disease is not an absolute requirement.

Pathogenesis

Calciphylaxis is a complex disease with multiple etiological factors. Although the disease pathogenesis remains unmasked, abnormal calcium and phosphorous metabolism,[9,10] inflammation[11] and the occurrence of a hypercoagulable state[9] have been seen and could result in vascular and extravascular calcification.

Some risk factors have been identified, including being female, Caucasian ethnicity, warfarin treatment, diabetes mellitus,

Address for correspondence: Dr. Shivangi Gupta, Private Practitioner, Chandigarh, India.
E-mail: shivangigupta69@gmail.com

Received: 26-07-2019 **Revised:** 20-08-2019 **Accepted:** 05-09-2019

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_588_19

How to cite this article: Baby D, Upadhyay M, Joseph MD, Asopa SJ, Choudhury BK, Rajguru JP, *et al*. Calciphylaxis and its diagnosis: A review. J Family Med Prim Care 2019;8:2763-7.

obesity, impaired calcium and phosphorus metabolism, hypoalbuminemia, prolonged dialysis.[12]

The pathogenesis of calciphylaxis remains unclear and is considered as complex disorder involving numerous etiological factors. Calciphylaxis is characterized by ischemic necrosis of skin resulting from calcification of tunica media and fibrotic changes in intima of the cutaneous arterioles along with thrombotic occlusion. Calciphylaxis was first described as disorder of hypersensitivity in rodents by Hans Selye wherein after sensitization by a calcifying factor resulted in local calcification, inflammation, and sclerosis.[13]

The process of calciphylaxis requires two main steps:[14]

1. Calcification of medial wall and intimal fibrosis of the arterioles.
2. Thrombotic occlusion resulting from progressive calcification and endothelial dysfunction. Vascular calcifications result due to dysfunction of the regulatory mechanisms that manage calcium, phosphate, and parathyroid hormone (PTH) levels. Dystrophic vascular calcification can either involve the tunica media or intima, along with or secondary to the formation of atherosclerotic plaques resulting in calcium hydroxyapatite and matrix vesicles deposition within the vessel walls.[15]

Role of Vascular smooth muscle cells in calciphylaxis

Another school of thought is that vascular calcification begins with the differentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like phenotypes.[14] VSMCs normally produce matrix gla protein (MGP), a protein that binds calcium phosphate and thus has a strong inhibitory effect on tissue calcification. Vitamin K antagonists are thought to reduce functional MGP, as they interfere in the vitamin K carboxylation by which MGP is normally activated. Vitamin K antagonists lead to under-carboxylation of MGP thus lack of activated MGP leads to medial calcification.[16]

Role of osteoprotegerin (OPG)

Receptor activator of NF-kB ligand (RANKL) is expressed by osteoblasts and stromal stem cells that binds to its receptor, RANK, on the surface of osteoclasts and their precursors. This regulates the differentiation of precursors into multinucleated osteoclasts and osteoclast activation resulting in increased bone resorption. Osteoprotegerin (OPG) is a soluble protein secreted by osteoblasts and osteogenic stromal stem cells and acts as a decoy receptor thus preventing the binding of RANKL to RANK, protects the skeleton from excessive bone resorption. According to the passive theory vascular calcification could result from arterial accumulation of matrix products liberated from uncontrolled osteoclast degradation of bone. In fact, in animal models with OPG deficit, extensive vascular calcification is observed due to the hyperactivity of the RANKL-RANK-NF-kB axis that also promotes the activation of bone morphogenic proteins 2 and 4 (BMP2 and BMP4) favoring the osteogenic transition of smooth muscle cells.[17]

Role of bone morphogenetic protein

Bone morphogenetic protein-4(BMP-4) and osteopontin that are considered to be the markers of osteoblastic transformation are also expressed in lesional tissue of patients with calciphylaxis.[18] The BMP-4 catalyzes the process of calcification via reactive oxygen species, that act through nuclear factor kappa B (NFkB).

Hypercoagulability and calciphylaxis

Hypercoagulability plays an important role in the development of calciphylaxis. The induction of local hypercoagulability may have an effect on prothrombotic regions. The factors linked to calciphylaxis enhance the process of thrombosis by reducing anti-thrombotic response or enhancing prothrombotic processes, as opposed to inducing calcification. However anti-thrombotic responses such as expression of C and S protein receptors, thrombomodulin expression and vascular heparin-like molecules that promote thrombosis are reduced by Inflammatory cytokines like IL 1,6, TNF-alpha.[15] Certain drugs like acenocoumarol also serve as an important risk factor in non-uraemic calciphylaxis patients.[16]

Clinical presentation and Diagnosis of calciphylaxis

Skin lesions are painful representing subcutaneous indurated nodules or plaques accompanied by livedo reticularis, often initially labelled dermis-hypodermis. The evolution is done in a few days towards the formation of superficial and then deep ulcerations leading to the constitution of a blackish eschar, always strongly painful with centrifugal extension.[19]

Intense pain associated with palpation of firm calcified subcutaneous tissue and cutaneous lesions is suggestive of calciphylaxis in dialysis patients and in patients with other risk factors for the disorder.[20,21] Patient history should be obtained and a thorough examination should be performed to identify additional skin lesions. In patients administering warfarin, distinction should be made between calciphylaxis and warfarin necrosis.[22]

Various steps that are undertaken for accurate diagnosis of the disease are as follows.

Physical examination

As mentioned earlier, the primary presentation of the disease is in form of symptomatic cutaneous painful lesions. On examination, these lesions initially present as serpiginous, tender, palpable subcutaneous masses later on progressing to non-healing ulcers.[23]

The lesions in calciphylaxis are painful and may be sometimes secondarily infected involving adipose rich sites of the trunk and lower extremities. These lesions appear as an indurated plaques overlaid by livedo racemosa that may progress to nonhealing, black stellate-shaped ulcers. The typical net like pattern of lesions is due to the cutaneous vasculature consisting of central arterioles running perpendicularly from vessels in the fascia. The

resulting cyanosis due to accumulation of deoxygenated blood at the junctional areas between these blood vessels lead to the classic net-like lesional configuration.[16]

Radiological tests and biomarkers

The clinical examination of a patient with calciphylaxis involves two important goals: to evaluate the presence of any etiological factor and to rule out any potential disorders that may mimic the physical examination findings.

Even plain X-rays, nuclear bone scans and circulating fetuin A levels have been reported to aid in the diagnosis, none of these tools have been recommended for clinical use.[24-26] Clinical imaging, chief among these plain X-rays and 3-phase nuclear bone scans are important diagnostic tools.[16]

Bone scan with single-photon emission computed tomography-computed tomography (SPECT-CT) help in localizing extent of the pathology and determine the areas of microcalcifications. The bone scan is positive when the tracer technetium 99 m-labeled medronic acid binds to hydroxyapatite crystals at the calcified areas in the dermis and subcutaneous fat.[27]

Compared to plain X ray, CT, and mammography, bone scan with SPECT-CT assesses the exact anatomical location and extent of the disease. Bone scan offers high sensitivity rate of 97% in cases of calciphylaxis and has the ability to survey the entire body.[28]

Raman spectroscopy

Diagnostic procedures like biopsy in calciphylaxis lesions are considered to be invasive, time consuming, and destructive as in these procedures due to the presence of calcified and blocked vessels blood flow to the debrided area decreases and furthermore these sites do not heal well. Radiographic techniques like CT scan can detect calcium deposits but are not specific for calciphylaxis and require further biopsy. Thus, a noninvasive and label free method (Raman spectroscopy) was introduced for detecting small calcifications within a large wound area.

Raman spectroscopy involves chemical fingerprinting of a sample with micron-level spatial resolution and subsurface probing in deep-red and near infrared regions in order to detect the carbonated apatite in calciphylaxis. Raman spectroscopy makes use of either a Raman microprobe (for tissue area of 0.4 mm × 0.7 mm) or a handheld fiber Raman probe (for tissue area <1 mm).

The main requirement in this diagnostic procedure is of a fiber-optic handheld probe that detects the carbonated apatite in calciphylaxis at various sites and depths. The probe must function despite varying tissue background, including contributions from serum, plaques, eschars, and lipids. Spectra must be collected in <2 s and ideally, no more than 1 s. With rapid measurements it is easy to map the wound area and characterize wound margins for treatment and debridement.[29]

Laboratory tests

Renal function test (FRT), including serum blood urea nitrogen, estimated glomerular filtration rate and serum blood creatinine should be conducted to further evaluate potential risk factors. Furthermore, bone mineral tests including, serum calcium, alkaline phosphatase, phosphorous, intact parathyroid hormone, and vitamin D evaluation can be done. Liver function test (LFT) including alkaline phosphatase, serum transaminase, and albumin. Patient's complete blood count (CBC) with differential count and blood cultures can be performed in order to rule out any infection. Coagulation prolife of the patients can be monitored by prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT). Hypercoagulation evaluation can be done by estimating protein C, S, antithrombin III and antiphospholipid antibody levels. Inflammation evaluation including, serum C-reactive protein (CRP) and albumin. Finally, evaluation of presence of autoimmune diseases and malignancy.[30]

Skin biopsy

Best way to confirm calciphylaxis requires biopsy of involved area of skin and the test should be preformed whenever the diagnosis is considered. There are some concerns related to skin biopsy need consideration including, notifying the patient of the risks and benefits of the procedure. Probable risks include propagation of new lesions, ulceration, superimposed infection, induction of necrosis, and bleeding. On the other hand, benefits of skin biopsy include ruling out other conditions that can mimic the disorder.[21]

A telescoping biopsy or a punch biopsy wedge skin biopsy are probably to have the most excellent yield.[31] The main histological characteristics of the skin are medial calcification, internal hypertrophy and associated with local inflammation resulting in vessel obstruction and cutaneous necrosis.[32,33]

While skin lesions are the major clinical signs of the disease, other organs such as the lungs, skeletal muscles, pancreas, brain, eyes, and digestive tract, could also develop calciphylaxis lesion.[30] Microscopic examination of micro-calcification frequently needs special stain such as von Kossa or Alizarin red. The use of these special stains increase the recognition of calcium deposit over individual stain alone, which should be thought when clinical suspension is high except calcium deposits are not obvious on routine histological sections.[34]

Lesional biopsy can demonstrate medial calcification and intimal proliferation of small vessels. Other diagnostic histopathological features are extravascular soft tissue calcification, septal and lobular panniculitis, dermal-epidermal split, and epidermal necrosis.[35] Another diagnostic feature highly specific for calciphylaxis is perieccrine calcification.

The diagnostic criteria based on biopsy sometimes indicate low sensitivity in patients where biopsy specimen lacks calcifications.

The possible reasons for the low sensitivity include:

1. Early stages of calciphylaxis may demonstrate a thrombotic vasculopathy of superficial dermal vessels, a finding associated with many hypercoagulable conditions.
2. Various procedural errors, errors during tissue processing, limited depth of specimen, etc., may contribute to low sensitivity.[35]

Further for obtaining sufficient biopsy sample an excisional biopsy or punch biopsy with a depth of 6-8 mm can be done. If necessary, at the base of large punch biopsy a telescoping 4 mm punch biopsy is done for obtaining sufficient tissue.[16]

Differential diagnosis

Calciphylaxis must be distinguished from a similar clinical condition like warfarin skin necrosis. The clinical features of both these diseases share common findings like involve painful skin ulcers and tend to affect the adipose rich sites. The two distinguishing features include the time of medication to the onset of skin lesions and the response to warfarin cessation. Warfarin skin necrosis responds immediately to warfarin discontution and presents within the first few days of drug usage, whereas calciphylaxis induced by warfarin requires longer duration usage before the lesion onset and the lesions of calciphylaxis persist much longer despite discontinuation of causative drugs.

Implications for clinical practice

The primary care physician is the first contact of a patient for the consultation of illness. Early diagnosis and a multi-disciplinary approach are key components of managing this complex disease. Calciphylaxis has no approved therapies and there are limited treatment modalities for calciphylaxis. Increased awareness and research in this field have facilitated identification of risk factors and causation pathways. Development of therapeutic options and wound care management, however, are still at a nascent stage. Certain therapies have shown a promise that needs evaluation in prospective clinical trials.[36]

In suspected cases of calciphylaxis in a uremic patient, the calcium phosphate product level should be normalized by increasing dialysis, using phosphate binders, reducing the calcium supply. In cases of secondary infection or ulcerations antibiotics are recommended. Pain reduction can be achieved using narcotic analgesics or fentanyl patches. Drugs like Sodium thiosulfate and bisphosphonates can also be used for treating calciphylaxis. Sodium thiosulfate increases the calcium solubility or combines with calcium to form dialyzable salt and has vasodilatation and antioxidant properties. As an antioxidant, sodium thiosulfate may neutralize reactive oxygen species that promote inflammation, thrombosis, and vasoconstriction. Vitamin K is also known to prevent the calcification in coronary arteries and hence act as a decalcifying agent. Deficiency of Vitamin K prevents MGP activation and consequently promotes vascular calcification.[27]

Conclusion

Calciphylaxis is a complex ischemic vasculopathy with various aetiological risk factors usually seen in patients suffering from renal disease and can also be diagnosed in patients with normal renal function. The disease detection relies on certain set clinical, histopathological and imaging criteria. In patients diagnosed positive for the disease must be taken care because of its increased mortality rate.

Financial support and sponsorship

Nil.

Conflict of interest

There is no conflict of interest.

References

1. Milas M, Bush RL, Lin P, Brown K, Mackay G, Lumsden A, *et al.* Calciphylaxis and nonhealing wounds: The role of the vascular surgeon in a multidisciplinary treatment. J Vas Surg 2003;37:501-7.
2. Bryant J, White W. A case of calcification of the arteries and obloterative endarterities, associated with hydronephrosis, in a child aged six months. Guys Hosp Rep 1898;55:17-20.
3. Selye H, Gabbiani G, Strebel R. Sensitization to calciphylaxis by endogenous parathyroid hormone. Endocrinology 1962;71:554-8.
4. Selye H. The dermatologic implications of stress and calciphylaxis. J Invest Dermatol 1962;39:259-75.
5. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy. Kidney Int 2002;61:2210-7.
6. Ketteler M. Case report. N Engl J Med 2001;345:1119-24.
7. Hussein MR, Ali HO, Abdulwahed SR, Argoby Y, Tobeigei FH. Calciphylaxis cutis: A case report and review of lilerature. Exp Mol Pathol 2009;86:134-5.
8. Fernandez M, Morales E, Gutierrez E, Polanco N, Hernandez E, Merida E, *et al.* Calciphylaxis: Beyond CKD-MBD. Nefrologia 2017;37:501-7.
9. Trost O, Kadlub N, Trouilloud P, Malka G, Danino A. Calciphylaxis: A severe but unrecognised complication in end-stage renal disease patients. A review of 2 cases. Ann Chir Plast Esthet 2005;50:746-50.
10. Imam AA, Mattoo TK, Kapur G, Bloom DA, Valentini RP. Calciphylaxis in pediatric end-stage renal disease. Pediatr Nephrol 2005;20:1776-80.
11. Slough S, Servilla KS, Harford AM, Konstantinov KN, Harris A, Tzamaloukas AH. Association between calciphylaxis and inflammation in two patients on chronic dialysis. Adv Perit Dial 2006;22:171-4.
12. Sowers K, Hayden M. Calcific uremic arteriopathy: Pathophysiology, reactive oxygen species and therapeutic approaches. Oxid Med Cell Longev 2010;3:109-21.
13. Bhambri S, Bhambri A, Dell Rosso JQ. Calciphylaxis: A review. J Clin Aesthetic Dermatol 2008;1:38-41.
14. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol 2008;19:213-6.
15. Jeong, Dominguez. Calciphylaxis: Controversies in

pathogenesis, diagnosis and treatment. Am J Med Sci 2016;351:217-27.

16. Wenstedt EFE, Huysentruyt CJ, Konings CJAM. Acenocoumarol as a risk factor for calciphylaxis: A feature clinicians should be aware of. Neth J Med 2017;75:161-4.
17. Cucchiari D, Torregrosa JV. Calciphylaxis in patients with chronic kidney disease: A disease which is still bewildering and potentially fatal. Nefrologia 2018;38:579-86.
18. Griethe W, Schmitt R, Jurgensen JS, Bachmann S, Eckardt KU, Schindler R. Bone morphogenic protein-4 expression in vascular lesions of calciphylaxis. J Nephrol 2003;16:728-32.
19. Fares I, Bouattar T, Kone HM, Benzouina H, Benbella M, Ouzeddoun N, *et al.* Calciphylaxis: Successful management of a rare complication of chronic kidney disease in two patients. Case Rep Nephrol 2019;2019:1-6.
20. Brewster U. Dermatological disease in patients with CDK. Am J Kidney Dis 2008;51:331-44.
21. Dauden E, Onate M. Calciphylaxis. Dermatol Clin 2008;26:557-68.
22. Nazarian R, Cott EV, Zembowiez A, Duncan L. Warfarin-induced skin necrosis. J Am Acad Dermatol 2009;61:325-32.
23. Rogers N, Teubner D, Coates P. Calcific uremic arteriolopathy: Advances in pathogenesis and treatment. Semin Dial 2007;20:150-57.
24. Schafer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, Floege J, *et al.* The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 2003;112:357-66.
25. Shmidt E, Murthy NS, Knudsen JM, Weenig RH, Jacobs MA, Starnes AM, *et al.* Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. J Am Acad Dermatol 2012;67:1296-301.
26. Han MM, Pang J, Shinkai K, Franc B, Hawkins R, Aparici CM. Calciphylaxis and bone scintigraphy: Case report with histological confirmation and review of the literature. Ann Nucl Med 2007;21:235-8.
27. Chang JJ. Calciphylaxis: Diagnosis, pathogenesis, and treatment. Adv Skin Wound Care 2019;32:205-15.
28. Martineau P, Pelletier-Galarneau M, Bazarjani S. The role of bone scintigraphy with single-photon emission computed tomography-computed tomography in the diagnosis and evaluation of calciphylaxis. World J Nucl Med 2017;16:172-4.
29. Lloyd WR, Agarwal S, Nigwekar SU, Esmonde-White K, Loder S, Fagan S. Raman spectroscopy for label-free identification of calciphylaxis. J Biomed Opt 2015;20:80501.
30. Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, *et al.* Calciphylaxis: Risk factors, diagnosis, and treatment. Am J Kidney Dis 2015;66:133-46.
31. Angelis M, Wong L, Myers S, Wong L. Calciphylaxis in patients on hemodialysis: A prevalence study. Surgery 1997;122:1083-9.
32. Rogers N, Coates P. Calcific uraemic arteriolopathy: An update. Curr Opin Nephrol Hypertens 2008;17:629-34.
33. Weenig R. Pathogenesis of calciohylaxis: Hans selye to nuclear factor kappa-B. J Am Acad Dermatol 2008;58:458-71.
34. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med 2018;378:1704.
35. Mochel MC, Arakaki RY, Wang G, Kroshinsky D, Hoang MP. Cutaneous calciphylaxis: A retrospective histopathologic evaluation. Am J Dermatopathol 2013;35:582-6.
36. Seethapathy H, Brandenburg VM, Sinha S, El-Azhary RA, Nigwekar SU. Review: Update on the management of calciphylaxis. QJM 2019;112:29-34.