Journal of Clinical and Medical Images

ISSN: 2640-9615

Case Report

Calciphylaxis, A Therapeutic Challenge

Terlizzi V[1*], Bertoni D[1] and Cancarini G[2,3]

[1]Department of Nephrology, ASST Spedali Civili di Brescia and Postgraduate School in Nephrology, University of Brescia, Italy

[2]Department of Nephrology Operative Unit, ASST Spedali Civili Brescia, Brescia, Italy

[3]Department of Medical and Surgical Specialties, Radiological Science and Public Health, University of Brescia, Brescia, Italy

Volume 2 Issue 4- 2019
Received Date: 13 Sep 2019
Accepted Date: 06 Oct 2019
Published Date: 12 Oct 2019

1. Abstract

Report on two cases of calciphylaxis a severe complication which can occur mainly in dialysis patients on oralanticoagulation therapy. Diagnosis and therapy of this disease are reviewed. The importance of prevention and early diagnosis and therapy is stressed.

2. Keywords

Calciphylaxis; Sodium thiosulphate; Dialysis; End stage renal disease

3. Case 1

H.R., 59-year-old patients, on hemodialysis in our centre since 2009 for End Stage Renal Disease (ESRD) due to glomerulopathy not histologically examined, was admitted to our Division for the appearance of multiple necrotic infiltrated lesion of the skin on the back, abdomen and legs. Those lesions were frankly suspicious for calciphylaxis (**Figure 1**). The levels of PTH, calcium and phosphorus before hospitalization were respectively 1658 pg/ml (reference values: 10-65 pg/ml), 9.3 mg/dL (r.v.: 8.2-10 mg/dl), and 5.9 mg/dl (r.v.: 3.5-4.5 mg/dl). She was taking Oral Anticoagulant Therapy (OAT) with vitamin K antagonists due to previous implantation of aortic mechanical valve. The patient was treated with cinacalcet 60 mg x 3/week but, despite various meetings with the physicians to improve adherence to therapy, her compliance was null.

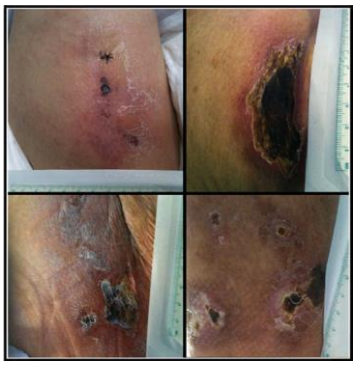

Figure 1: Case 1. Skin lesions

4. Case 2

F.R. was an 86-year-old patient on Continuous Ambulatory Peritoneal Dialysis (CAPD), since July 2015, due to ESRD probably secondary to diabetic nephropathy. She was admitted to our Ward because of the appearance of a necrotic skin lesion (**Figure 2**) on the right leg with important subcutaneous inflammatory infiltration and periareolar livedo reticularis on the right breast. Both lesions were suspected for calciphylaxis. Before hospitalization her laboratory tests were: PTH 757 pg/ml, serum calcium 8.1 mg/dl (Ca corrected for serum albumin 9.0 mg/dl), and phosphorus 3.5 mg/dl. The patient was taking the following medications: calcitriol, cholecalciferol and Oral Anticoagulation Therapy (OAT) due to for atrial fibrillation.

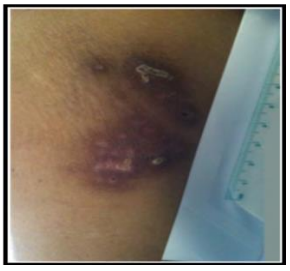

Figure 2: Case 2. Skin lesions.

Corresponding Author (s): *Vincenzo Terlizzi, Department of Nephrology, ASST Spedali Civil di Brescia and Postgraduate School in Nephrology, University of Brescia, Italy, Tel: +39-030-3995626, Fax: +39-030-396663, E-mail: vinciterli@libero.it*

Citation: Terlizzi V, Calciphylaxis, A Therapeutic Challenge. Journal of Clinical and Medical Images. 2019; V2(2): 1-5.

5. Calciphylaxis Overview

Calciphylaxis is a rare but severe condition that can afflict patients suffering from chronic kidney disease, although cases have been described in not uremic patients [1]. Prevalence in dialysis patients is between 1% and 4%[2]. Prognosis is very poor with a one-year mortality rate ranging from 45% to 80%, mainly due to sepsis of ulcerated lesions of Calciphylaxis[3].

The clinical presentation of the skin lesions is heterogeneous: it can manifest as *livedo reticularis*, purple mesh, purplish plaques or nodules which progress to necrosis and ulceration and, finally, eschar formation [4].

Lesions are often located in regions of the skin that lie on a thick layer of subcutaneous fat such as buttocks, thighs and abdominal wall. The biopsy of these lesions shows calcification, fibrointimalmicrothrombosis and hyperplasia of small arteries and arterioles of the dermis and subcutaneous layer that cause ischemia and panniculitis of the underlying fat layer.

Skin biopsies should be stained with Von Kossa and Alizarin red which are able to identify calcium deposits in the media layer of the vessels, coloring these deposits, respectively, in black and red-orange [5].

The pathogenesis of calciphylaxis is not fully understood. Vascular calcification, one of the main challenges in chronic kidney disease, affects many patients and worsens both morbidity and mortality. The pathogenesis consists in the calcification of the vessel's tunica media which is associated with endothelial lesions and dysfunction resulting in a reduction in the vessel calibre that reduces blood flow. Finally, this condition causes a hypercoagulable state with ischemia downstream of the area affected [6].

Calciphylaxis is considered the result of changes in calcium-phosphate metabolism due to chronic kidney disease. The main risk factors are: secondary hyperparathyroidism, hyperphosphatemia, active vitamin D intake and high calcium-phosphate product (Ca x P). Fortunately, although these conditions are often present in dialysis patients, there is no high prevalence of calciphylaxis. The explanation of this probably lies in the fact that other mechanisms are necessary for the development of calciphylaxis. The deficit of proteins that inhibits tissue calcification such as fetuin-A and matrix Gla protein (MGP) may increase the risk of calciphylaxis. Fetuin concentrations in blood decrease in case of inflammation; further support for the role of inflammation is given by the occurrence of calciphylaxis in patients with Crohn's disease and systemic lupus erythematosus [7,8]. MGP is a K-dependent vitamin protein, so vitamin K antagonists such as oral anticoagulants reduce its concentrations thus increasing the risk of calciphylaxis[9].

Other diseases associated with calciphylaxis are: diabetes mellitus, obesity, hypercoagulable status (deficiency of protein C or S, antithrombin, antiphospholipid syndrome, cryofibrinogenemia), alcoholic hepatitis, dialytic vintage and malnutrition. Some drugs contribute to increase the risk of calciphylaxis: the Vitamin K antagonists mentioned above, calcium supplements, calcium-based phosphate binders, active vitamin D supplements, corticosteroids and subcutaneous injections of heparin and insulin due to local trauma [10].

Since the hypothesized pathogenetic mechanisms of calciphylaxis act systemically and not only in the skin, clinical manifestations also occur in other organs: Calciphylaxis causes pain, severe myositis and rhabdomyolysis in muscles. In the central nervous system it can cause dementia or stroke while in the lungs a respiratory failure can be caused by metastatic calcifications. Calcification also occur in the cardiac conduction system and cause atrioventricular blocks and cardiac valve dysfunction. There may also be calcifications of pancreatic and adrenal glands and involvement of the gastrointestinal system with ischemia and bleeding [11,12-14].

Diagnosis is based on the biopsy of the lesions; however, the usefulness and safety of such procedure is questioned when the clinical picture is unequivocal. After biopsy, there is a potential risk of new lesions in case of ulceration, infection, bleeding and necrosis after biopsy [10]. Moreover, biopsy finding is sometimes not conclusive due to inadequate sampling.

6. Therapy

6.1. Removal of Risk Factors

One of the early intervention to cure calciphylaxis consist in the removal of some hypothesized pathogenetic factors. The mineral bone metabolism should be targeted to the range recommended by KDIGO CKD-MBD guidelines [15]. It can be obtained by substituting calcium-based phosphate binders with non-calcium containing phosphate binders, by avoid high calcium concentration in the dialysis bath and by starting a therapy with cinacalcet[16].

Some authors have proposed calciphylaxis as an indication of parathyroidectomy, but the results published so far are conflicting [17]. If the patient is being treated with oral anticoagulants vitamin K antagonists should be suspended and, if indicated, be initiated therapy with low molecular weight heparin in appropriate dose for anticoagulation. In addition, vitamin K therapy should be initiated at high doses; this therapy does not increase the thrombotic risk, but guarantees an adequate supplementation for MGP that inhibits calcification. Left atrial auricular closure was proposed in with atrial fibrillation to allow the interruption of oral anticoagulant therapy.

6.2. Topical Treatment

Wound management should be based on a multidisciplinary approach between nephrologist, nurses and plastic surgeon. Several reports did not shown a significant benefit in the invasive approach, which can cause a greater risk of infection and worsening of the lesion[18].

In our experience the lesions benefit from a treatment that will have to be modulated according to their severity and extent. For ulcers and necrotic eschar, it is preferable to associate a local treatment based on collagenase dressing with gauze soaked in paraffin and hyaluronic acid. For less extensive but not yet necrotic lesions with intense subcutaneous infiltration is useful topical therapy with corticosteroids and antibiotics and boric water.

6.3. Systemic Therapy

Sodium thiosulfate (STS) therapy was first used by Cicone et al. in 2004 [19]. Since then, it from since has become the most commonly used therapy to treat calciphylaxis even if it is an off-label indication [20]. Its properties as reducing agent make it able to form soluble complexes with many metals. Although there is not a standard dose of STS for the treatment of calciphylaxis, the effective doses reported in the literature vary from 5 to 25 g given intravenously in saline 3 times a week, during or after the dialysis session [21].

Side effects reported in the literature include nausea, vomiting, metabolic acidosis, hypotension and fluid overload [22]. Recently it has also been proposed intralesional injection of STS [23] or prescription administration PO [24].

STS has antioxidant, vasodilator and chelation properties; it acts as an antioxidant by removing reactive species implicated in the pathogenesis of calciphylaxis and by generating glutathione. Vasodilation is ensured by an increased synthesis of nitric oxide synthase and other vasodilating agents. Chelation of intravascular and intraparenchymal calcium salts by STS produces calcium thiosulphate, which is significantly more soluble than other calcium salts and can be removed by dialysis.

Hyperbaric therapy has been proposed as an aid in the treatment of calciphylaxis as it can stimulate proliferation of fibroblasts and conversion to myofibroblasts (useful in wound healing), stimulate angiogenesis and arteriolar vasoconstriction to prevent edema, reperfusion injury and wound infections [25]. Patients can benefit from 20-30 treatments cycles of 100-110 minutes at a pressure of between 2.0 and 2.4 atm[26]. Hyperbaric therapy is associated with some, although rare, risks as barotrauma that could involve ears, sinuses and lungs, temporary worsening of myopia, claustrophobia, and seizures related to the toxicity of high concentrations oxygen [26]. For these reasons as well as fact that patients with by calciphylaxis are usually affected by several comorbidities it's not always possible to perform the treatment in a hyperbaric chamber.

Use of corticosteroids is also controversial; some authors suggest them to reduce systemic inflammation [27], others [28] consider the use of corticosteroids as risk factor to development of calciphylaxis. Although use of bisphosphonates is limitated in patients with advanced renal failure, there are some experience of their use in calciphylaxis with good result in pain management, albeit with a limited series [29,30]. Pain management in this type of patients is of primary importance; the pharmacological groups, opioids included, should be used to improve the quality of life of these patients.

7. Case Study 1

The OAT was suspended and LMWH initiated at anticoagulant dosing. A skin biopsy confirmed the suspicion of calciphylaxis. The dose of cinacalcet was increased to 60 mg/die and sodium thiosulfate 25g, 3 times a week after HD was started: In addition, vitamin K supplements, pain therapy with opioids and topical treatment for major injuries. During the hospitalization there was no evidence of clinical improvement of skin lesions. After 24 days the patient developed, sudden acute abdomen with radiological CT evidence of sigmoid colon perforation requiring urgent surgery and left hemicolectomy. After 56 days of hospitalization the patient, died as a result of septic shock. Histological analysis on the colon has highlighted extensive calciphylaxis. (**Figure 3**) The intestinal wall was characterized by ischemic colitis with a perforated acute diffuse visceritis. In the intima-media of many medium and small caliber vessels of mesocolon there were circumferential calcium deposits with obliteration of the vessel lumen of

8. Case Study 2

The patient was suffering from type 2 diabetes since 1980, hypertension since 2000, atrial fibrillation since October 2014 (with onset with acute embolic ischemia of the lower limbs bilaterally).

A skin biopsy confirmed the suspicion of calciphylaxis with evidence in the hypodermic adipose tissue of calcified material in the wall of some vessels and of calcium deposits in the adipocytes. (**Figure 4**)

OAT was stopped and LMWH started, with supplements of vitamin K, cinacalcet and STS (25 g of STS 3 times a week at the end of dialysis infused in 250 ml of 5% glucose solution.). The topical lesion was treated with poultices of boric water, diflucortolone cream and fusidic acid ointment.

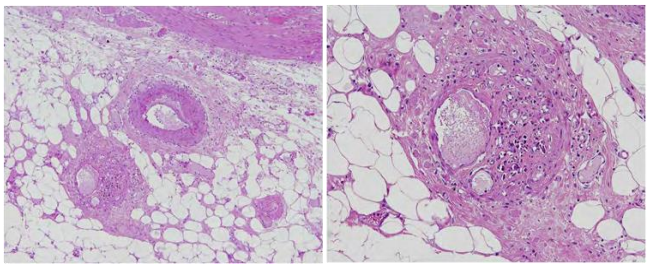

Figure 3: Vessels with thickened and calcified wall in perivisceral (gut) adipose tissue; hematoxylin and eosin (20x and 40x).

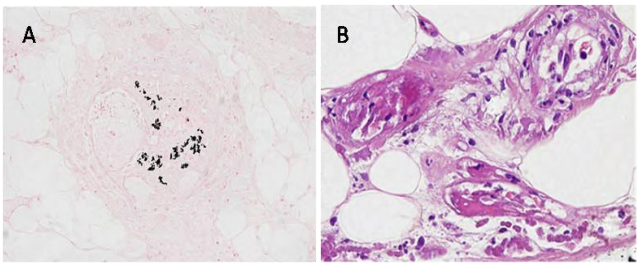

Figure 4: Panel A: Von Kossa staining histochemistry showing black calcium deposits (40x). Panel B: Hematoxylin-eosin staining; vessel calcification in subcutaneous tissue (40x).

The patient was proposed to perform sessions of hyperbaric therapy, but she, unable to tolerate the oxygen mask, was terrified by the hyperbaric chamber.

An esophagogastroduodenoscopy and colonoscopy showed chronic gastroduodenitis and previous infectious colitis. Colonic biopsies did not show evidence of vascular calcifications.

Clinically, there has been an improvement of the injury and pain. The patient was discharged in fair general conditions and planned sessions of infusion of STS as outpatient.

9. Conclusion

Calciphylaxis is difficult to manage; it imposes and early diagnosis and therapy and should be prevented by early treatment of abnormal calcium-phosphate metabolism in patients on dialysis.

References

1. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from non-uremic causes: a systematic review. Clin J Am SocNephrol. 2008; 3(4):1139-1143.

2. Esteve V, Almirall J, Luelmo J, Saez A, Andreu X, Garcia M. Calcific uraemicarteriolopathy (calciphylaxis): incidence, clinical features and long term outcomes. Nefrologia. 2007; 27(5): 599-604.

3. Nigwekar SU. Calciphylaxis.Curropinnephrolhypertens. 2017; 26(4): 276-281.

4. Dauden E, Onate MJ. Calciphylaxis.Dermatologic clinics. 2008; 26(4): 557-568.

5. Mochel MC, Arakaki RY, Wang G, Kroshinsky D, Hoang MP. Cutaneouscalciphylaxis: a retrospective histopathologic evaluation. Am J Dermatopatholo. 2013; 35(5): 582-586.

6. Au S, Crawford RI. Three-dimensional analysis of a calciphylaxis plaque: clues to pathogenesis. J Am AcadDermatolo.2002; 47(1): 53-57.

7. Barri YM, Graves GS, Knochel JP.Calciphylaxis in a patient with Crohn's disease in the absence of end-stage renal disease.Am j kidney dis. 1997; 29(5): 773-776.

8. Sakr SH, Russell EB, Jasin HE. Systemic lupus erythematosus and calciphylaxis.Journal rheumatol.2004; 31(9): 1851-1853.

9. Yu WY, Bhutani T, Kornik R, Pincus LB, Mauro T, Rosenblum MDet al. Warfarin-Associated NonuremicCalciphylaxis. JAMA dermatolo.2017; 153(3): 309-314.

10. Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson V et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am j kidney dis. 2015; 66(1): 133-146.11.

11. Randall DP, Fisher MA, Thomas C. Rhabdomyolysis as the presenting manifestation of calciphylaxis.Muscle nerve.2000; 23(2): 289-293.

12. Matsuo T, Tsukamoto Y, Tamura M, Hanaoka M, Nagaoka T, Kobayashi Y et al. Acute respiratory failure due to "pulmonary calciphylaxis" in a maintenancehaemodialysis patient. Nephron.2001; 87(1): 75-79.

13. Li YJ, Tian YC, Chen YC. Fulminant pulmonary calciphylaxis and metastatic calcification causing acute respiratory failure in a uremic patient.American journal of kidney diseases.2006; 47(4): e47-53.

14. Kloeppel R, Luebke P, Mittag M, Achenbach H, Stephan S, Kluge Ret al. Acute hypercalcemia of the heart ("bony heart"). J computassist tomogr.2001; 25(3): 407-411.

15. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD).Kidney intSuppl.2009; (113): S1-130.

16. Russell R, Brookshire MA, Zekonis M, Moe SM. Distal calcific uremic arteriolopathy in a hemodialysis patient responds to lowering of Ca x P product and aggressive wound care. Clinical nephrology.2002; 58(3): 238-243.

17. Lal G, Nowell AG, Liao J, Sugg SL, Weigel RJ, Howe JR. Determinants of survival in patients with calciphylaxis: a multivariate analysis. Surgery.2009; 146(6): 1028-1034.

18. Martin R. Mysterious calciphylaxis: wounds with eschar--to debride or not to debride? Ostomy wound manage.2004; 50(4): 64-66.

19. Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate.Am j kidney dis.2004; 43(6): 1104-1108.

20. Peng T, Zhuo L, Wang Y, Jun M, Li G, Wang L et al. A systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients.Nephrology (Carlton, Vic). 2017; 23(7): 669-675

21. Ackermann F, Levy A, Daugas E, Schartz N, Riaux A, Derancourt C et al. Sodium thiosulfate as first-line treatment for calciphylaxis. Archives of dermatology.2007; 143(10): 1336-1337.

22. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E, Jr. Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clinical journal of the American Society of Nephrology.2013; 8(7): 1162-1170.

23. IsoherranenK, Bouchard L, Kluger N. Benefits of intralesional injections of sodium thiosulfate in the treatment of calciphylaxis. Int wound j.2017; 14(6): 955-959.

24. Shetty A, Klein J. Treatment of Calciphylaxis: A Case for Oral Sodium Thiosulfate. Advperit dial.2016; 32: 51-55.

25. Aihara S, Yamada S, Uchida Y, Arase H, Tsuchimoto A, Nakano T et al. The Successful Treatment of Calciphylaxis with Sodium Thiosulfate and Hyperbaric Oxygen in a Non-dialyzed Patient with Chronic Kidney Disease. Intern med, 2016; 55(14); 1899-1905.

26. An J, Devaney B, Ooi KY, Ford S, Frawley G, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: A case series and literature review. Nephrology.2015; 20(7): 444-450.

27. Elamin EM, McDonald AB. Calcifying panniculitis with renal failure: a new management approach. Dermatology.1996; 192(2): 156-159.

28. Farah M, Crawford RI, Levin A, Chan Yan C.Calciphylaxis in the current era: emerging 'ironic' features? Nephrology, dialysis, transplantation. 2011; 26(1): 191-195.

29. da Costa JB, da Costa AG, Gomes MM.Pamidronate as a treatment option in calciphylaxis. JEurAcadDermatoloVenereolo.2008; 22(9): 1128-1130.

30. Torregrosa JV, Sanchez-Escuredo A, Barros X, Blasco M, Campistol JM. Clinical management of calcific uremic arteriolopathy before and after therapeutic inclusion of bisphosphonates.Clinnephrol. 2015; 83(4): 231-234.