



EFFECTIVE SODIUM THIOSULPHATE THERAPY IN CALCIPHYLAXIS

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Abstract. Calciphylaxis is a life-threatening complication of hemodialysis involving calcium deposition in media of hypodermic arteries and skin necrosis. With current unsatisfactory treatment, the calcium chelator and antioxidant sodium thiosulphate emerges as a possible new therapy. We report the case of a dialysis patient with parathyroidectomy for secondary hyperparathyroidism complicated by severe hypoparathyroidism and hypocalcemia, requiring sustained Ca and vitamin D treatment. Within a year, typical calciphylaxis developed on the breasts, associated with extensive calcification of medium-sized arteries on mammography. Cessation of calcium load and aggressive wound care led to no improvement. Sodium thiosulphate 25g thrice weekly for 2 months resulted in dramatic healing. Besides unusual location on the breasts, onset of lesions in the setting of an adynamic bone is noteworthy and probably favored by calcium load. This is, to our knowledge, the first use of sodium thiosulphate in calciphylaxis associated to low bone turnover, a valuable therapeutic asset since unlike in hyperparathyroidism, other treatment options lack. Also this is the first use of sodium thiosulphate for treatment of calciphylaxis in Romania, the drug being prepared in our University.

Keywords: calciphylaxis, sodium thiosulphate, low bone turnover, hemodialysis, breast necrosis

Introduction

Calciphylaxis is a life-threatening complication encountered in hemodialysis patients, involving calcium deposition within media of small hypodermic arteries, and dry ischemic necrosis of the surrounding skin. Calcific uremic arteriopathy (CUA) seems to be more frequent than previously believed, increasing by a rate of 4.5/100 patient-years in the past years [1] and reaching a prevalence of 4% among dialysis patients [2], findings that match our experience [3]. The majority of patients have high parathormone (PTH) levels and increased Ca-phosphate products [4-7], however, other risk factors are currently being considered [1, 8-11]. The

clinical picture includes violaceous painful skin lesions, which rapidly progress to ulcerations. When these develop, the mortality exceeds 90% [13] the main cause of death being uncontrolled sepsis due to infected wounds. The mainstay of treatment is aggressive management of calcium-phosphate metabolism in hyperparathyroid patients and intensive wound care, but results are inconsistent. The increasing prevalence of this condition, occurrence in non hyperparathyroid patients and the currently deceiving standard therapeutic approach, all drive the research for better therapies, one of these being the cation chelating and antioxidant agent sodium thiosulphate (STS).

Materials and methods

We report the case of a 54 year old woman, on dialysis for 9 years who developed severe secondary

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hyperparathyroidism (PTH 1385 pg/ml), the control of serum phosphate only being obtained with the aid of aluminum containing phosphate binders. She finally underwent subtotal parathyroidectomy which resulted in very low persistent PTH (2 pg/ml) and severe hypocalcaemia (corrected Ca 6 mg/dl) treated with active vitamin D (mean 1.15 µg/day), calcium supplementation (mean 1620 mg/day excluding diet, but as high as 3770 mg/day occasionally) and by the use of a 1.75 mmol/l Ca dialysis solution. After approximately one year on this regimen she developed painful bilateral asymmetric progressive violaceous lesions, on both of her breasts, followed shortly by dry necrosis with a typical aspect of calciphylaxis (figure 1). Skin biopsy was inconclusive but mammography showed extensive calcification

previous management was undertaken. Not being commercially available, a watery solution containing 25% STS (NATRII THIOSULFAS $\text{Na}_2\text{S}_2\text{O}_3 \times 5 \text{H}_2\text{O}$ Mr.248.2 - 3164.55mEq/l or 1582.27mmol/l) was prepared in our university's laboratory of infusions. The substance was dissolved in distilled water for infusions, the resulting solution being then filtered through a cartridge of cellulose acetate (Sartobran P 523 1507 H8- B). The filtering procedure was sterilizing and the solution was conditioned under a laminar air flow in borosilic glass bottles (INFUS.ISO 100 ml, type 2, 34358 37 001), sealed with special rubber stoppers (bromobutyl, type V9240, FM 257/5 SAF 1 001) and then capped with aluminum caps (type AM 3207 CTO 0059). Finally the solution was sterilized in steam water under



Figure 1. Calciphylaxis lesions (a) at diagnosis, (b) after conservative treatment (c) after 1 month of STS treatment, (d) after 3 months of STS treatment

of medium-sized arteries.

Vitamin D and calcium supplements were stopped and aggressive wound care was undertaken, using hydrocolloid, alginate and polyurethanic film dressings under surgical supervision, but the lesions worsened progressively over the course of three months. With the informed consent of the patient, treatment with STS, with no other change in the

pressure (by keeping the bottles in an autoclave for twenty minutes at 120°Celsius). The drug was given in the postdialysis setting, over an hour, diluted in 250 ml of saline solution 12.5 g trice weekly in the first week and 25 g trice weekly thereafter for a total of three months. The patient experienced no side effects, excepting an insidious onset of nausea in the third month of administration which

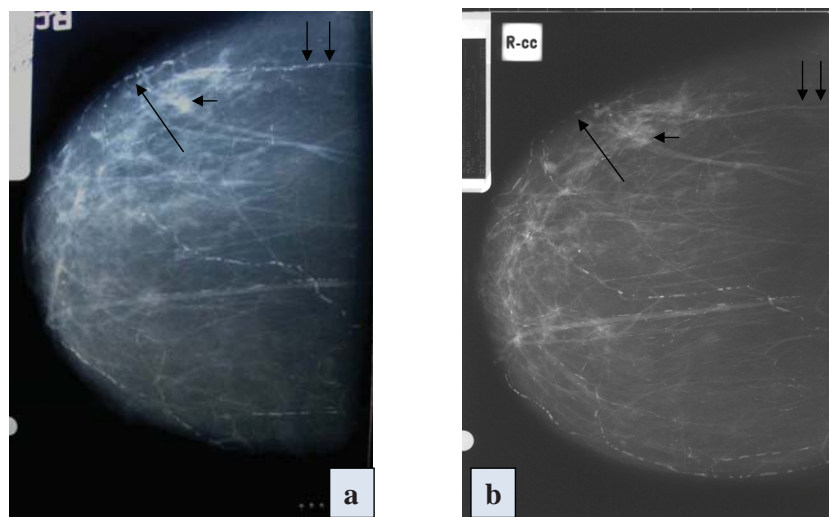


Figure 2. Mammography (a) at diagnosis, (b) at the end of treatment

was successfully treated with antiemetics. Dramatic improvement of the pain (within 1 week) was followed by progressive healing.

Interestingly, mammographic findings also improved, at least in some areas (figure 2).

Discussion

This case is particular in three aspects. First, the location of lesions on the breasts is unusual. To our knowledge there are only few case reports for calciphylaxis on the breasts, the majority in end stage renal failure patients with hyperparathyroidism [14-17]. Second, the onset of lesions after parathyroidectomy is also noteworthy. Calciphylaxis is usually associated to hyperparathyroidism but some cases in patients with low bone turnover states, even following parathyroidectomy have also been reported [18-20]. In fact, the rise of prevalence of calciphylaxis, paralleling overall improved control of hyperparathyroidism but increased low bone turnover disease could be tale telling. In our patient, the possible aluminum bone toxicity, associated with high doses of calcium and vitamin D after parathyroidectomy could have favored the ectopic calcification characteristic of calciphylaxis. In fact, increased calcium load from high dialysis calcium solution [21] or oral calcium [22, 23], has been identified as a risk factor for calciphylaxis.

No specific successful therapy has been identified for management of calciphylaxis not associated to hyperparathyroidism. STS is a cation chelating agent formerly used as a therapeutic agent in cyanide intoxication, cisplatin toxicity and topical treatments of acne and versicolor and, except for

gastrointestinal disorders, it is not toxic. STS is an effective antioxidant agent but also has the properties of a chelator of cations that renders calcium salts very soluble, therefore favoring their dissolution. It has been successfully employed in treatment of urolithiasis [24], and ectopic calcification in hemodialysis patients [25]. Several case reports have found significant reduction in ectopic tumoral calcinosis (both radiological and clinical improvement being noted) after long-term administration of sodium thiosulphate in hemodialysis patients [26, 27]. Noteworthy one of these is a case report on a patient without hyperparathyroidism, with low bone turnover due to aluminium bone deposition.

The use of STS in the setting of calciphylaxis is recent and limited to case reports [28-31]. Pain alleviates first, probably due to restoration of endothelial dysfunction and amelioration of oxidative stress in the subcutaneous capillary beds and the peripheral neuronal units involved [28]. Pain relief is followed by improvement and eventually by wound healing. When used in doses of 12.5-25 g 3-4 times weekly STS administration was generally devoid of side effects. Duration of therapy varied from a few weeks to several months, long term use has also been reported [31]. Facing rapid improvement of the clinical picture, in our patient STS was stopped by the end of the third month of treatment.

This is, to our knowledge, the first case report of calciphylaxis associated with low bone turnover in Romania, the first reported use of STS in our country and, last but not least the first use of STS in calciphylaxis associated with low bone turnover. Its calcium chelating and antioxidant properties qualify STS as an excellent first choice treatment

option for this severe potentially lethal condition of hemodialysis patients, and more so in cases not associated to hyperparathyroidism, in which specific therapy directed to high bone turnover is lacking [28]. Nevertheless, specific clinical trials regarding the use of STS in calciphylaxis are needed for definitive management recommendations.

Bibliography

1. **Fine A, Zacharia J.** Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002; **61**:2210-2217.
2. **Angelis M, Wong LL, Myers SA, Wong LM.** Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery* 1997; **122**:1083-1090.
3. **Kacso I, Rusu A, Racasan S, Patiu IM, Orasan R, Rogojan A, Georgescu C, Airizer M, Moldovan D, Spanu C, Vladutiu D, Gherman Caprioara M.** Calcific uremic arteriopathy related to hyperparathyroidism secondary to chronic renal failure. A case control study. *Acta endocrinologica* 2008, **4**:391-400.
4. **Roe SM, Graham LD, Brock WB, Barker DE.** Calciphylaxis: early recognition and management. *J Am Surg* 1994; **60**:81-86.
5. **Duffy A, Schurr M, Warner T, Chen H.** Long-term outcomes in patients with calciphylaxis from hyperparathyroidism. *Ann Surg Oncol* 2006; **13**:96-102.
6. **Galimberti RL, Farias Edos R, Parra IH, Algranti L, Kowalczuk A, Imperiali N, Greloni GC, Galimberti G.** Cutaneous necrosis by calcific uremic arteriopathy. *Int J Dermatol* 2005; **44**:101-106.
7. **Levin A, Metha RL, Goldstein MB.** Mathematical formulation to help identify the patient at risk of ischemic tissue necrosis - a potentially lethal complication of chronic renal failure. *Am J Nephrol* 1993; **13**:448-453.
8. **Ruggian JC, Maesaka JK, Fisbane S.** Proximal calciphylaxis in four insulin requiring diabetic haemodialysis patients. *Am J Kidney Dis* 1996; **28**:409-414.
9. **Bleyer AJ, Choi M, Igezie B, del Torre E, White WL.** A case control study of proximal calciphylaxis. *Am J Kidney Dis* 1998; **32**:376-383.
10. **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**:171-174.
11. **Coates T, Kirkland GS, Dymock RB, Murphy BF, Brealey JK, Mathew TH, Disney AP.** Cutaneous necrosis from calcific uremic arteriopathy. *Am J Kidney Dis* 1998; **32**:384-391.
12. **Padovan C, Bonfigli F, Ulessi B, Gottardi C, Giansante C, Trevisan G.** Calciphylaxis of the breast: a rare disease in the differential diagnosis of breast cancer. *Acta Dermatovenerol Croat* 2008; **16**(2):83-86.
13. **Bonilla LA, Dickson-Witmer D, Witmer DR, Kirby W.** Calciphylaxis mimicking inflammatory breast cancer. *Breast J* 2007; **13**:514-516.
14. **Kouba DJ, Owens NM, Barrett TL, Laman SD.** An unusual case of calciphylaxis. *J Cutan Med Surg* 2004 **8**:19-22.
15. **Patetsios P, Bernstein M, Kim S, Mushnick R, Alfonso A.** Severe necrotizing mastopathy caused by calciphylaxis alleviated by total parathyroidectomy. *Am Surg* 2000, **66**:1056-1058.
16. **Loynes JT.** A rare cause of breast necrosis. Calciphylaxis. *Postgrad Med* 1999, **106**:161-162.
17. **Mawad HW, Sawaya BP, Sarin R, Malluche HH.** Calcific uremic arteriopathy in association with low turnover uremic bone disease. *Clin Nephrol* 1999; **52**:160-166.
18. **Matsuoka S, Tominaga Y, Uno N, et al.** Calciphylaxis: a rare complication of patients who required parathyroidectomy for advanced renal hyperparathyroidism. *World J Surg* 2005, **29**:632-635.
19. **Elder G, Kumar K.** Calciphylaxis associated with chronic kidney disease and low bone turnover: management with recombinant human PTH-(1-34) *NDT Plus* 2008, **1**:97-99.
20. **Llach F.** The evolving pattern of calciphylaxis: therapeutic considerations, *Nephrol Dial Transplant* 2001, **16**:448-451.
21. **Campistol JM, Almirall J, Martin E, Torres A, Revert L.** Calcium-carbonate induced calciphylaxis. *Nephrol* 1989, **51**:549-550.
22. **Zacharias JM, Fintaine B, Fine A.** Calcium use increases risk of calciphylaxis: a case-control study. *Perit Dial Int* 1999, **19**:248-252.
23. **Yatzidis H.** Successful sodium thiosulphate treatment for recurrent calcium urolithiasis. *Clin Nephrol* 1985, **23**:63-67.
24. **Yatzidis H, Agroyannis B.** Sodium thiosulfate treatment of soft-tissue calcifications in patients with end-stage renal disease. *Peritoneal Dial Bull* 1987, **7**:250-2.
25. **Papadakis JT, Patrikarea A, Digenis GE, Stamatelou K, Ntaountaki I, Athanasopoulos V, Tamvakis N.** Sodium thiosulfate in the treatment of tumoral calcifications in a hemodialysis patient without hyperparathyroidism. *Nephron* 1996, **72**(2):308-12.
26. **Kyriakopoulos G, Kontogianni K.** Sodium thiosulfate treatment of tumoral calcinosis in patients with end-stage renal disease. *Ren Fail* 1990, **12**(4):213-9.
27. **Hayden MR, Tyagi SC, Kolb L, Sowers JR, Khanna R.** Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriopathy: the emerging role of sodium thiosulfate. *Cardiovasc Diabetol* 2005, **4**:4-10.
28. **Cicone JS, Petronis JB, Embert CD, Spector DA.** Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis* 2004, **43**:1104-1108.
29. **Meissner M, Bauer R, Beier C, Betz C, Wolter M, Kaufmann R, Gille J.** Sodium thiosulphate as a promising therapeutic option to treat calciphylaxis. *Dermatology* 2006, **212**:373-376.
30. **Bruculeri M, Cheigh J, Bauer G, Serur D.** Long-term intravenous sodium thiosulfate in the treatment of a patient with calciphylaxis. *Semin Dial* 2005; **18**:431-434.