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Successful Treatment of Severe Iatrogenic Calcinosis Cutis with Intravenous Sodium Thiosulfate in a Child Affected by T-Acute Lymphoblastic Leukemia

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Abstract: **Sodium thiosulfate has been successfully used to treat calcyphilaxis in adults and children, but its effect on iatrogenic calcinosis cutis secondary to extravasation of calcium solutions is less known. We describe a 5-year-old boy with acute lymphoblastic leukemia who developed severe calcinosis cutis in the right forearm and hand, and in the left leg and foot after extravasation of calcium gluconate during treatment for tumor-lysis-syndrome-related hypocalcaemia. Surgical debridement, local wound care, hyperbaric oxygen therapy, and sodium thiosulfate infusion achieved a complete healing of all lesions in an eight-month period with a short discontinuation of chemotherapy. No functional or sensitive impairment remained.**

Iatrogenic calcinosis cutis can occur after extravasation of calcium containing solutions (1,2), with extensive calcium deposition in the derma and necrotic ulceration (1–3). Conservative measures such as elevation of the extremity, application of cold packs and wound care with local injection of sodium sulfate or triamcinolone acetonide have been effective in cases with superficial lesions (1). Hyperbaric oxygen therapy (HOT) coupled with sodium thiosulfate (STS) have been used to treat diffuse calcyphylaxis related to end-stage renal disease (4,5), but their use in iatrogenic calcinosis cutis has not been reported. We describe a case of a 5-year-old boy with calcinosis cutis due to extravasation of calcium gluconate. The extensive lesions in the right hand and forearm, in the left leg and foot failed to improve with local wound care and HOT but recovered completely after introduction of intravenous (i.v.) STS.

CASE REPORT

A 5-year old boy was diagnosed a T-cell acute lymphoblastic leukemia (T-ALL). Main clinical findings at presentation were: hyperleukocytosis (white blood count 20.9×10^9/L), peripheral blastosis (7.52×10^9/L),

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hepatosplenomegaly, mediastinal mass, and right pleural leukemic effusion. After thoracentesis and positioning of Argyle-tube drainage, the patient was started on prednisone according to induction treatment of AIEOP protocol for T-ALL (6). After 3 days of prednisone, he developed a severe tumor lysis syndrome (TLS) with hyperphosphoremia, hyperkaliemia, hyperuricemia, hypocalcemia and acute renal failure that required hemodialysis for 2 days. Intubation and mechanical ventilation were also necessary for 2 days to control respiratory distress. The patient received other supportive measures for TLS (rasburicase, allopurinole, furosemide) and adequate alkaline hydration. TLS-related hypocalcemia was treated by 10% calcium gluconate solution i.v. infusion at a dose of 2–3 mL/kg/day for 9 days and subsequently reduced to 1–0.5 mL/kg/day for 6 days until normalization of calcium serum levels. In addition, he received calcium carbonate 3 g/day over 4 days by nasogastric tube.

During the first day of treatment, calcium gluconate solution was administered through a peripheral vein. Two episodes of extravasation occurred involving first the right forearm and hand and then the left foot causing skin erythema, oedema, pain, swelling and eventually ulcer and eschar. Main biochemical parameters at the time of extravasation were: urea 39.4 mmol/L (n.v. 1.80–6.40 μmol/L), creatinine 124 μmol/L (n.v. 27–62 μmol/L), uric acid 0.35 mmol/L (n.v. 0.12–0.32), LDH 3979 U/L (n.v. 0–600), pH 7.4, K + 6.7 mmol/L (n.v. 3.4–4.5 mmol/L), Na + 130 mmol/L (n.v. 136–145 mmol/L), Cl– 85 (n.v. 96–108), Ca 1.30 mmol/L (n.v. 2.20–2.70 mmol/L), and P 7.77 mmol/L (n.v. 1.45–1.78 mmol/L). Doppler ultrasound of both extremities excluded venous thromboses. The lesions were treated conservatively (limb elevation, daily wound care, and warm compresses) while phase 1a of induction chemotherapy was completed.

After 51 days from extravasation, the child was re-admitted to the hospital for fever and worsening of the lesions with increasing pain, progressive joint ankylosis (right elbow and wrist, left ankle) and functional impairment, hardening and fibrosis of tissues surrounding the necrotic ulcers and lymphangitis. The culture obtained from the eschar of the left limb showed infection by *Staphylococcus epidermidis* and *Enterobacter cloacae* therefore intravenous antibiotic therapy with meropenem, teicoplanine, and amikacin was performed for 21 days. In addition to wound cleaning, disinfection, and physiotherapy, the patient was started on daily HOT and weekly surgical debridement and escharectomy whilst phase Ib of induction was substituted by a less intensive chemotherapy (4 pulses of vincristin and prednisone over 1 month).

On day 83 after extravasation, after 1 month of HOT and aggressive surgical wound care, no significant improvement of limb eschars was observed and soft tissues hardening became more extended involving the entire right arm, the distal half of the left leg, the dorsal part of the ankle and foot (Fig. 1). Imaging studies (radiograph and CT scan) and biopsy of the eschar confirmed that the hardening was due to calcification of soft-tissues deep to the bones (Figs. 2A and 3A).

Given the massive calcification with motility impairment, treatment with i.v. STS 10 g/dose (435 mg/kg) three times a week was added whilst full-dose chemotherapy was resumed with four courses of high-dose methotrexate (5 g/m^2). Beginning from day 100 after extravasation, the patient presented a progressive improvement of the lesions with appearance of tissue regeneration on the bottom of the eschar and reduction of eschar size, softening of surrounding tissues and borders. After 6 months from extravasation and 3 months from starting STS, the eschars were almost completely healed (Fig. 4) with a massive reduction of soft-tissue

Figure 1. Right upper limb and left lower limb on day 83 after extravasation, before starting sodium thiosulfate treatment.

Figure 2. Arm radiograph: (**A**) before sodium thiosulfate treatment; (**B**) after 3 months of sodium thiosulfate treatment.

Figure 3. Leg radiograph: (**A**) before sodium thiosulfate treatment; (**B**) after 3 months of sodium thiosulfate treatment.

calcifications (Figs. 2B and 3B). This was associated with a complete functional recovery of both limbs. His ALL remains in complete hematological remission after 13 months from diagnosis.

Overall, the patient received 56 HOT treatments over 4 months and 45 doses of STS over 5 months while surgical wound care was continued for 7 months, although less frequently in the last 4 months. STS treatment was well tolerated and nausea was well controlled with ondansetron 5 mg/m^2.

DISCUSSION

Our patient developed extensive and severe iatrogenic skin calcinosis after extravasation of calcium gluconate during induction treatment for T-ALL. Skin calcinosis is normally considered a self-limited condition that, without underlying metabolic disturbances, tends to resolve with local wound care in 2–6 months (1). In our patient, however, skin lesions progressed and worsened in a 2-month period despite the normalization of serum calcium level, the suspension of calcium supplementation and the frequent surgical wound care with HOT. This suggests that some alteration of calcium metabolism at cellular and tissue level could be present in leukemia and may contribute to the pathogenesis of calcinosis cutis in this disease (7). In fact calcinosis cutis has been described in leukemic patients in association with hypercalcemia (7,8) and urolithiasis has also been described during prednisone treatment for leukemia even with normal serum calcium levels (9). We therefore suppose that factors other than calcium extravasation alone may have enhanced calcinosis cutis in our patient (10). Extravasated calcium could have triggered local tissue injury and inflammation, causing further cellular calcium release while tissue and cellular changes induced by concurrent chemotherapy and infection could have amplified this reaction (11) making it resistant to conventional treatment.

STS has been shown to be a promising and successful agent in treating calcinosis in end-stage renal disease adult patients (4,5) and in calcific uremic arteriolopathy in children (12). Given the similar chemical nature of the calcium deposits in those diseases and in calcinosis cutis we reasoned that STS might also be useful in the treatment of our patient's severe iatrogenic calcinosis cutis. To our knowledge no cases have been reported on the use of STS in leukemic patients for the treatment of extensive iatrogenic calcinosis cutis even though STS use is well known in oncology as an antidote for mechloretamine and cisplatin extravasations (13) and pediatric schedules have been used to prevent carboplatin toxicity in limited case series (14). Proper toxicity profiles are not yet known for children, but nausea, vomiting and mild hypernatremia have been the only adverse effects observed at the used doses of 10–16 g/m^2 (14).

Even if the patient was receiving HOT and intensive medical and surgical treatment, a clear improvement of clinical and radiological picture occurred only after the

Figure 4. Right upper limb and left lower limb after 6 months of sodium thiosulfate treatment.

initiation of STS therapy. This chronological correlation suggests that STS has significantly contributed to the healing of all skin lesions. Two mechanisms could be taken into account to explain this improvement: the enhancement of the solubility of calcium deposits and the subsequent mobilization of calcium from affected tissues by STS and its antioxidant effect that restores endothelial cell function (15). In fact, STS is a chelator of cations and calcium thiosulfate is an extremely high soluability compound resulting in inhibition of precipitation of calcium salts and in dissolution of calcium deposits (12–16). STS is also an antibrowning, reducing, and antioxidant agent that readily donates electrons to repair unpaired damaging electrons with a positive effect on endothelial nitric oxide generation promoting vasodilation and therefore vascularization of both the soft tissues and the peripheral neuronal unit involved in calcification (15,16). The child experienced indeed both soft tissue softening and appearance of tissue regeneration on the bottom of the eschar after STS treatment was started. He could also be withdrawn from narcotics due to rapid relief of pain, probably referable to the positive effect of STS on the oxidative stress and the vascularization of the peripheral neuronal units.

We conclude that STS is a useful therapeutic option for iatrogenic calcinosis in ALL patients and enhances the activity of standard combined multidisciplinary medical and surgical approaches such as pain and infection management, local wound care, surgical debridement, and HOT. Moreover, STS is well tolerated and its administration does not interfere with the administration of chemotherapy treatment.

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REFERENCES

1. Moss J, Syrengelas A, Antaya R et al. Calcinosis cutis: a complication of intravenous administration of calcium glucanate. J Cutan Pathol 2006;33(Suppl 2):60–62.
2. Domizio S, Puglielli C, Barbante E et al. Calcinosis cutis in a newborn caused by minimal calcium gluconate extravasation. Int J Dermatol 2006;45:1439–1440.
3. Lin CY, Hsieh KC, Yeh MC et al. Skin necrosis after intravenous calcium chloride administration as a complication of parathyroidectomy for secondary hyperparathyroidism: report of four cases. Surg Today 2007;37:778–781.
4. Meissner M, Bauer R, Beier C et al. Sodium thiosulphate as a promising therapeutic option to treat calciphylaxis. Dermatology 2006;212:373–376.
5. Meissner M, Kaufmann R, Gille J. Sodium thiosulphate: a new way of treatment for calciphylaxis? Dermatology 2007;214:278–282.
6. Conter V, Aricò M, Valsecchi MG et al. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) acute lymphoblastic leukemia studies, 1982–1995. Leukemia 2000;14:2196–2204.
7. Lestringant GG, Masouyé I, El-Hayek M et al. Diffuse calcinosis cutis in a patient with congenital leukemia and leukemia cutis. Dermatology 2000;200:147–150.
8. Tan AW, Ng HJ, Ang P et al. Extensive calcinosis cutis in relapsed acute lymphoblastic leukaemia. Ann Acad Med Singapore 2004;33:107–109.
9. Howard SC, Kaplan SD, Razzouk BI et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003;17:541–546.
10. Rodríguez-Cano L, García-Patos V, Creus M et al. Childhood calcinosis cutis. Pediatr Dermatol 1996;13:114–117.
11. Hasselgren PO. Catabolic response to stress and injury: implications for regulation. World J Surg 2000;24:1452–1459.
12. Araya CE, Fennell RS, Neiberger RE et al. Sodium thiosulfate treatment for calcific uremic arteriolopathy in children and young adults. Clin J Am Soc Nephrol 2006;1:1161–1166.
13. Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. Semin Oncol 2006;33:139–143.

14. Neuwelt EA, Gilmer-Knight K, Lacy C et al. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. Pediatr Blood Cancer 2006;47:174–182.
15. Cicone JS, Petronis JB, Embert CD et al. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. Am J Kidney Dis 2004;43:1104–1108.
16. Hayden MR, Tyagi SC, Kolb L et al. Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. Cardiovasc Diabetol 2005;1:4.