

Transient severe metastatic calcification in acute renal failure

Daniel Landau · Hanna Krymko · Hanna Shalev ·
Svetlana Agronovich

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Abstract Metastatic calcification, a known complication of prolonged end-stage renal disease, is herein described for the first time in a 10-month-old boy with acute renal failure, manifesting as a painful and swollen arm. Imaging revealed diffuse calcification and technetium-99 methylene diphosphonate ($^{99}\text{Tc-MDP}$) uptake around the humerus and axilla. Calcium and vitamin D restriction, followed by intravenous administration of sodium thiosulfate caused a full symptomatic, radio- and scintigraphic improvement.

Keywords Hemolytic uremic syndrome · Calcific uremic arteriopathy · Sodium thiosulfate · Radionuclide imaging · Peritoneal dialysis · Alfacalcidol

Abbreviations

ARF acute renal failure
HUS hemolytic uremic syndrome
MC metastatic calcifications
ST sodium thiosulfate

Introduction

Vascular (“metastatic”) calcification (MC) (or calcific uremic arteriopathy) is the most common type of extra-

osseous calcification in end stage renal disease, manifesting as both medial and intimal calcification of large arteries [1]. It usually results from a deposition of calcified products in otherwise normal tissues as a result of hyperphosphatemia with or without hypercalcemia. It may affect the visceral organs, such as kidneys, lungs, and gastric mucosa, as well as joints, eyes, and skin [2]. The predisposing conditions of hyperphosphatemia and high (calcium \times phosphorus) concentration products need to be persistent over weeks and months, since MC has been not been described in the setup of acute renal failure (even though a similar biochemical profile is seen there too).

We describe a case of MC in a 10-month-old child presenting with hemolytic uremic syndrome (HUS) and acute renal failure (ARF).

Case report

A 10-month-old male infant was recovering from his first episode of atypical HUS. He belonged to a Bedouin tribe previously diagnosed by us [3] with recessive factor H deficiency. His clinical course was remarkable for microangiopathic hemolytic anemia, oliguric renal failure and hypertension with a depressed myocardial function, associated with resistant hypocalcemia (total calcium as low as 5.4 mg/dl) and hyperphosphatemia (as high as 13 mg/dl). The latter was eventually controlled with phosphor binders (aluminum hydroxide at first for several days and, later, calcium gluconate), intravenous administration of calcium (mainly due to an episode of cardiac arrest without hyperkalemia, as previously described for HUS [4]), low phosphorus diet and alphacalcidol, 0.25 μg q.d. (the latter only after serum phosphorus had been normalized). Medications were given through a right femoral vein

D. Landau (✉) · H. Krymko · H. Shalev
Department of Pediatrics A, Soroka University Medical Center,
P.O. Box 151, Beer-Sheva 84101, Israel
e-mail: ldaniel@bgu.ac.il

S. Agronovich
Department of Nuclear Medicine,
Soroka University Medical Center, Faculty of Health Sciences,
Ben Gurion University of the Negev,
Beer Sheva, Israel

catheter and peripheral veins in the right arm. Peritoneal dialysis was started, using regular calcium (3.5 meq/l) dialysate. Fresh frozen plasma (20 ml/kg) was given daily until there was evidence of HUS remission, and was then switched to 20 ml/kg twice a week, as previously done in homozygous factor H-deficient children [5].

Ten days after hospitalization, he was found to have a painful and mildly swollen left arm, mainly in the elbow area, with flexion limitation. There was no intravenous device in this arm. There were no high fever, local redness or swollen joints. The plain X-ray did not reveal any lesions or fractures. A week later the left shoulder and humeral area were more swollen and tender, with no specific nodule or bone deformity. On physical examination, the swelling was deeper than the dermis (mainly in the humeral area) and painful. The superficial skin did not show signs of ischemia, necrosis, ulceration or livedo reticularis. This time the plain X ray revealed diffuse calcification, involving mostly the arm muscles and the axilla (Fig. 1a). Calcium and phosphorus levels were 9.9 mg/dl and 6.6 mg/dl, respectively. Renal function remained stable but impaired (serum creatinine and urea concentrations were as low as 1.05 mg/dl and 90 mg/dl, respectively). Parathyroid hormone (PTH) levels were normal (25.7 pg/ml). Renal sonogram showed no evidence of nephrocalcinosis. A bone scan revealed significant technetium-99 methylene diphosphonate ($^{99}\text{Tc-MDP}$) uptake along the areas that had seemed to be affected on the X-rays and physical examination (Fig. 1b). Treatment with peritoneal dialysis, alphacalcidol and calcium salts was stopped. Ketoconazole 1 mg/kg per day was given for 3 days, in addition to prednisolone 2 mg/kg per day for a week. Renal function improved, but the ($\text{Pi} \times \text{Ca}$) products remained above $60 \text{ mg}^2/\text{dl}^2$. No improvement in the arm lesion was seen. On day 25 of hospitalization, intravenously administered sodium thiosulfate, 100 mg/kg q.d., was started for 12 days. A gradual symptomatic improvement in arm range of movement and resolution of local pain was seen. At follow-up 8 weeks afterwards, X-ray and bone scan revealed significant resolution of MC (Fig. 2). At long-term (>12 months) follow-up, no recurrence of MC was seen, in spite of recurrent events of HUS, eventually needing periods of peritoneal and hemodialysis.

Discussion

The unique MC features in our patient were its appearance early after the diagnosis of renal failure and its transient nature. Evidence for such early appearance of this complication comes only from an animal model of ARF (adenine-induced renal failure in rats), where microscopic metastatic calcification in aorta, coronary artery and other soft tissues were found after

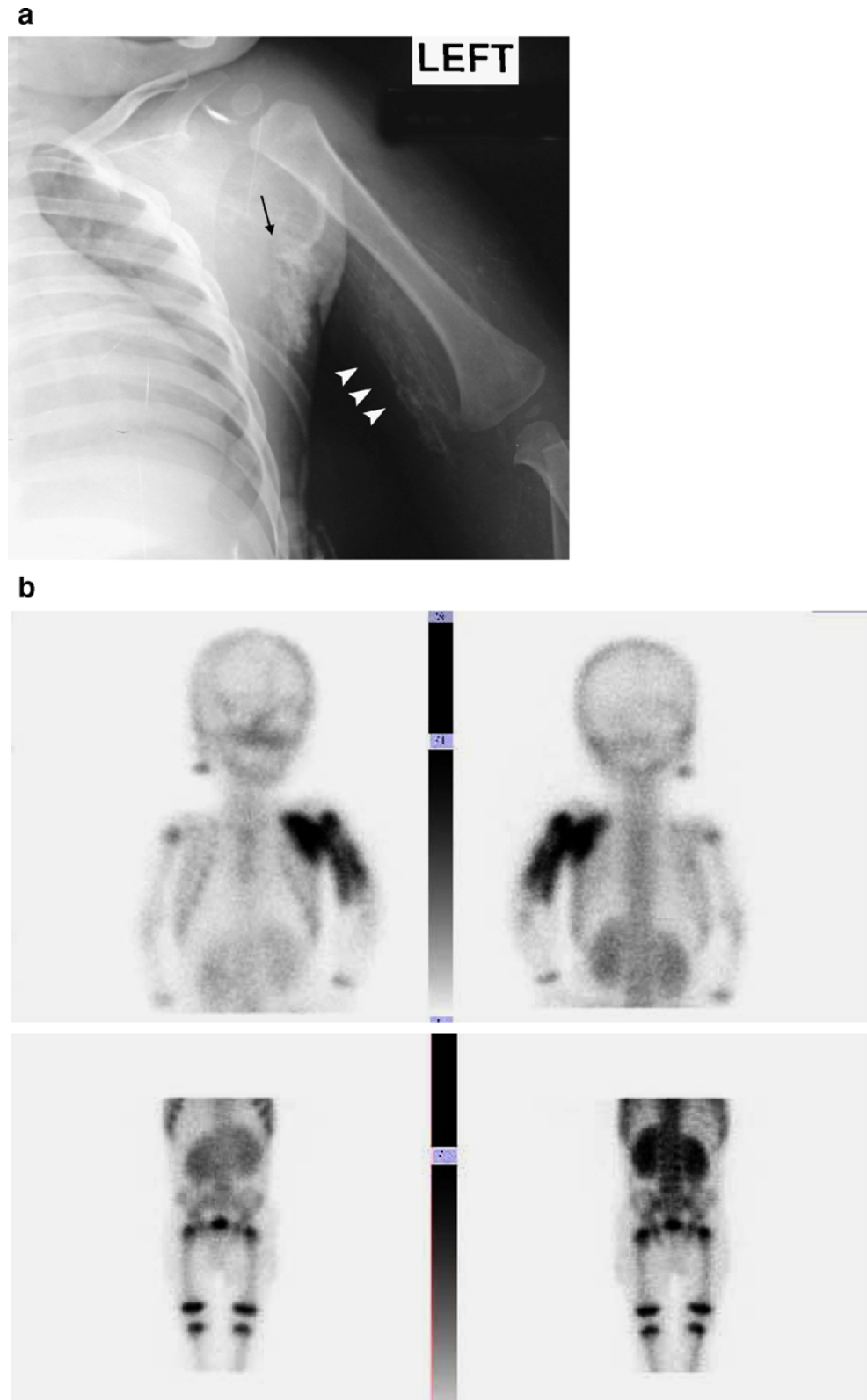
4 weeks of uremia [6]. This was associated with hyperparathyroidism, hypocalcemia and hyperphosphatemia. In addition, a high index of suspicion may detect the MC early in the renal failure course, before it becomes ulcerated [7].

Current sophisticated imaging techniques suggest an incidence of subclinical or asymptomatic MC in 20–100% of patient with end-stage renal disease (ESRD) [8]. MC with soft tissue involvement in acute renal failure, to the best of our knowledge, has not been reported in children: using the PubMed and MESH search systems, and the terms “calcinosis” and “kidney failure, acute” (the term “calciophylaxis” is not an official indexing term), we found only three case reports of adults with such combination. There was a combination of risk factors for MC in our patient, including high dose parenteral calcium administration via both intravenous and peritoneal dialysis; high serum phosphorus levels due to renal failure and the hemolytic state; and the use of alphacalcidol [9]. These may have led to MC so early in the course of his disease. The possible correlation between renal failure due to HUS, a state where the basic damage is to the endothelium in small vessels, and MC is not supported by the literature search. Uremic calcification was thought to be a largely physico-chemical process facilitated by elevated $\text{Ca} \times \text{P}$ (i.e., “metastatic” calcification). Evidence now shows that vascular smooth muscle cells actively take up phosphate to form bio-apatite. This process is associated with a phenotypic transformation of vascular smooth muscle cells during which they express osteoblast markers [10].

Soft tissue accumulation of $\text{Tc}^{99\text{m}}$ MDP may be due to passive localization of tracer in slow fluid spaces (ascites, pleural effusion) when the blood concentration of tracer is high and these spaces do not clear as rapidly as the blood pool. Tracer may also bind in necrotic tissues (myositis, myonecrosis). Other causes of metastatic calcification include hypercalcemia from widespread destruction of bone (from metastatic cancer), parathyroid neoplasm and hypervitaminosis D. When the solubility product of calcium and phosphate is exceeded, there is precipitation of calcium in the extracellular space. Soft tissue calcification is, thus, another cause of soft tissue uptake of $\text{Tc}^{99\text{m}}$ MDP [11].

Reported therapeutic strategies for treating and preventing MC include: increasing dialysis dose, lowering serum calcium phosphorous and $\text{Ca} \times \text{P}$ solubility products, and avoiding calcium-based Pi binders and vitamin D analogs. Unfortunately, these methods have been ineffective in some patients with MC. Intravenously administered sodium thiosulfate (ST) increases the solubility of calcium deposits [12]. ST was shown to be successful in the treatment of both nephrolithiasis and tumoral calcinosis. ST has antioxidant effects on endothelial cells, but its exact mechanism of effect is unclear. It undergoes mainly renal clearance. Its half-life is increased from 15 min in the normal glomerular

Fig. 1 Chest X-ray on day 18 (a) *black arrow* calcification on the axilla, *arrowheads* calcification lines along the humerus. Tc-^{99m} MDP scintigraphy (b) shows increased abnormal uptake in the soft tissue of the left shoulder, humerus and left scapula. Kidneys are enlarged, with increased diffuse abnormal radiotracer activity



filtration rate (GFR) to 478 min in dialysis-dependent patients. The recommended adult dose is 12.5–25 g at the end of dialysis. The duration of this treatment is unclear. In

our patient, a short ST course plus the withdrawal of enteral calcium and vitamin D were sufficient to resolve MC, which did not recur in the following events of HUS.

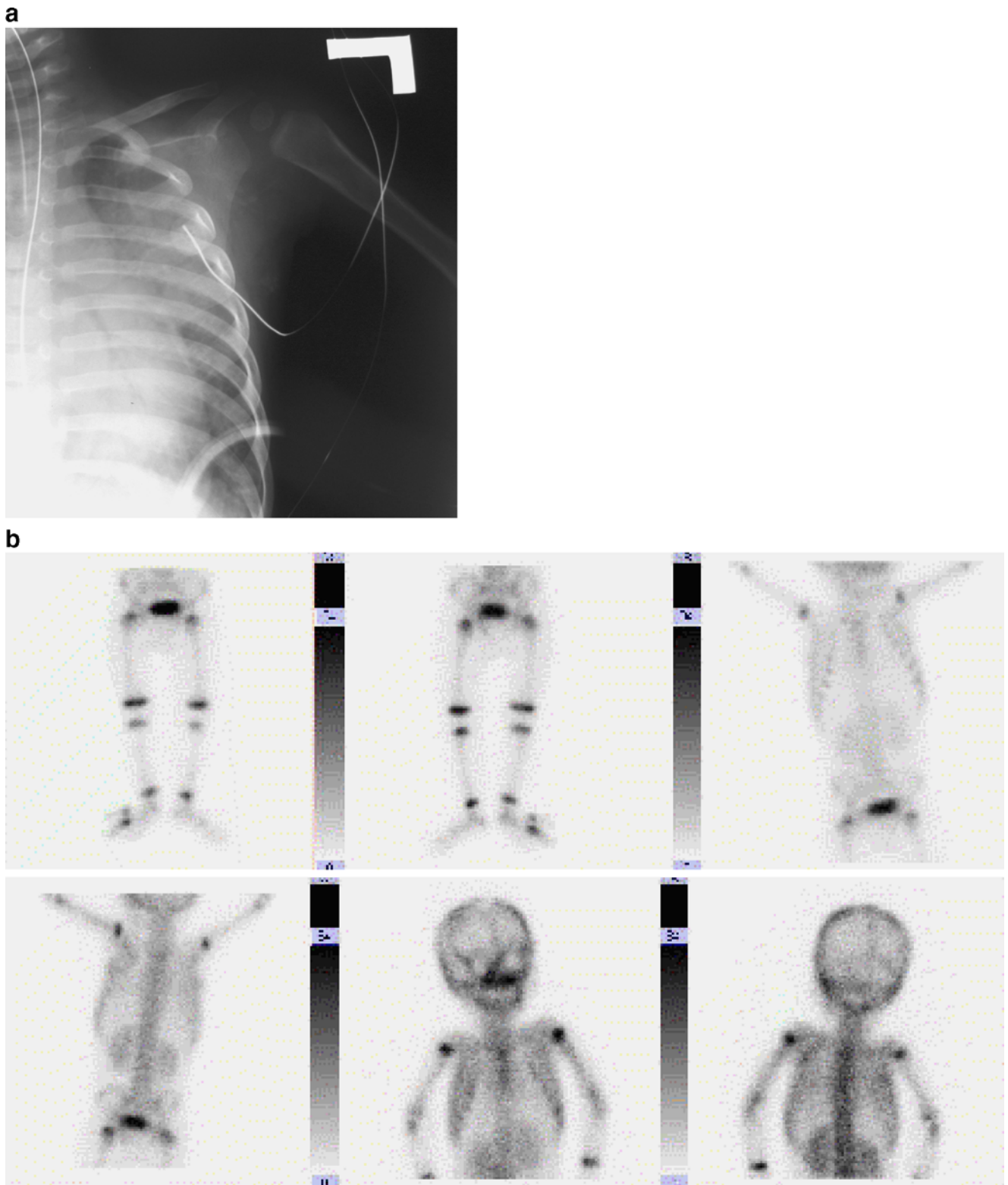


Fig. 2 Repeated X-ray (**a**) and bone scan (**b**) after 1 month show no abnormal findings

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