Clinical Case Report

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A case report of pediatric calciphylaxis–a rare and potentially fatal under diagnosed condition

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Abstract

Rationale: Though to be rare, calcific uremic arteriolophathy (CUA) is an ectopic calcification entity causing pain and disabilities in patients with chronic renal insufficiency, thus increasing the morbidity and mortality.

Patient concern: We report a case of four years old boy admitted with acute respiratory failure. Physical examination revealed: irritability, purple subcutaneous hard nodules, tachypnea, dry spasmodic cough, respiratory rate 45/min, heart rate 110/min, blood pressure 100/60 mmHg, with normal heart sounds, no murmurs, hepatomegaly with hepato-jugular reflux. He was diagnosed at 2 years old with stage 5 chronic kidney disease due to untreated posterior urethral valve, and subsequently started peritoneal dialysis. He developed severe renal osteodystrophy, refractory to standard phosphate binders.

Diagnoses: Pathology examination revealed the presence of diffuse calcifications involving the skin, brain, heart, lung, kidney, stomach and pancreas, consistent with the underlying diagnosis of CUA.

Intervention: Apart from standard treatment for end stage renal disease and associated co-morbidities, intensive care procedures have been initiated: oxygen therapy, continuous positive airway pressure, inotropic medication (Dopamine, Dobutamine), anticonvulsants (Diazepam), and antiedematous therapy (Dexamethasone).

Outcome: His pulmonary function rapidly deteriorated up to the severe hypoxemia, seizures and cardio-respiratory arrest, despite the initiation of intensive care measures.

Lessons: A careful follow up of small children might detect in time an abnormal urinary pattern. The diagnosis of growth failure should also trigger urgent further investigation.

Abbreviations: Ca = serum calcium, CPAP = Continuous positive airway pressure system, CUA = calcific uremic arteriolophathy, ESRD = end stage renal disease, IgE = immunoglobulin E, PO_4 = serum PO_4, PTH = parathyroid hormone.

Keywords: calciphylaxis, children, diffuse calcifications, end-stage renal disease, secondary hyperparathyroidism

1. Introduction

Calcific uremic arteriolopathy (CUA) is a rare disease, with an incidence that does not exceed 5% in the adult population with end stage renal disease (ESRD). Histologic studies describe specific lesions of proliferative and calcifying endarteritis, associated with wide spread calcifications nodules in patients with end stage kidney disease.[1] Up to 90% of the calciphylaxis lesions occur at the lower limbs, with proximal lesions in 44% to 68% of patients.[2] In the pediatric population, an increased risk in males with ESRD and secondary hyperparathyroidism, with frequent distal extremity and visceral organ involvement, as well as an increased resistance to medical treatment has been noticed.[1] We report a pediatric patient with ESRD who developed systemic CUA after 2 years of peritoneal dialysis, a co-morbidity eventually leading to his death. Ethical approval from our Hospital Ethics Committee has been obtained prior to publication of this case report.

2. Case report

A 4-year and 8-month old Caucasian boy was admitted with pulmonary distress associated with dry cough, malaise, and irritability. The child was diagnosed with ESRD at age 2, due to untreated posterior urethral valve and subsequent urinary tract infections. Peritoneal dialysis has been initiated along with standard drug treatment (calcium carbonate 1000 mg 3 times a day, eritropoetine 1000 UI 3 time weekly, calcitriol 0.5 mcg once a day, iron 20 mg daily, renal multivitamins with 5 mg of folic acid once daily). Despite the 2 years of an uneventful schedule of peritoneal dialysis the disease outcome was negative, due to development of secondary hyperparathyroidism and renal osteodystrophy (Table 1). This ended up in limping and difficulty to walk despite the continuous calcium carbonate supplementation (as phosphate binder) and calcitriol. The proposal to replace

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Table 1

Average serum calcium (Ca), serum phosphorus (PO_4), calcium–phosphate product (Ca × PO_4), parathyroid hormone (PTH), obtained throughout age 2 to 3.

Year/age	Serum calcium, mg/dL	Serum PO_4, mg/dL	Ca × PO_4, mg^2/dL^2	Alkaline phosphatase, UI/L	PTH, pg/mL
2012 (2 years)	9,45	7,34	71,56	722	567
2013/ 01 (2 years and 6 months)	11.22	10.88	118,76	1230	650
2013 /08 (3 years)	12,18	7,01	85,38	890	757
2014 /01 (3 years and 6 months)	10,81	8,56	92,53	870	620
2014 /08 (4 years)	12,15	9,29	112,87	1320	765
2014 / 11 (3 years and 3 months)	11,22	10,88	112,07	1860	940

calcium carbonate therapy with other phosphate binder (lanthanum carbonate, in association with calcitriol) was refused by the family. He always had an elevated calcium–phosphorus product, the highest being 118, 76 mg^2/dL^2 with a co-responding PTH level of 650 pg/mL (n = 10–65 pg/mL).

At 4 years and 6 months old, he presented with asthma like symptoms, (chest tightness, shortness of breath, dry cough, and wheezing) predominantly at night. An elevated IgE (1665 UI/mL) have been noted. Specific treatment with leukotriene inhibitors was added, with poor an outcome: as persistent dry cough.

In the following 2 months, he experienced a progressive deterioration of his nutritional status (with weight loss of 3 kg in 2 months), anemia, hypoproteinemia, and low cholesterol.

Currently, the physical examination revealed: irritability, very painful, hard, purple subcutaneous nodules, located at the level of the nasal pyramid, thorax, and abdomen (Fig. 1A). He also had tachypnea, dry spasmodic cough, respiratory rate 45/min, heart rate 110/min, blood pressure 100/60 mm Hg, with normal heart sounds, no murmurs, hepatomegaly with hepato-jugular reflux.

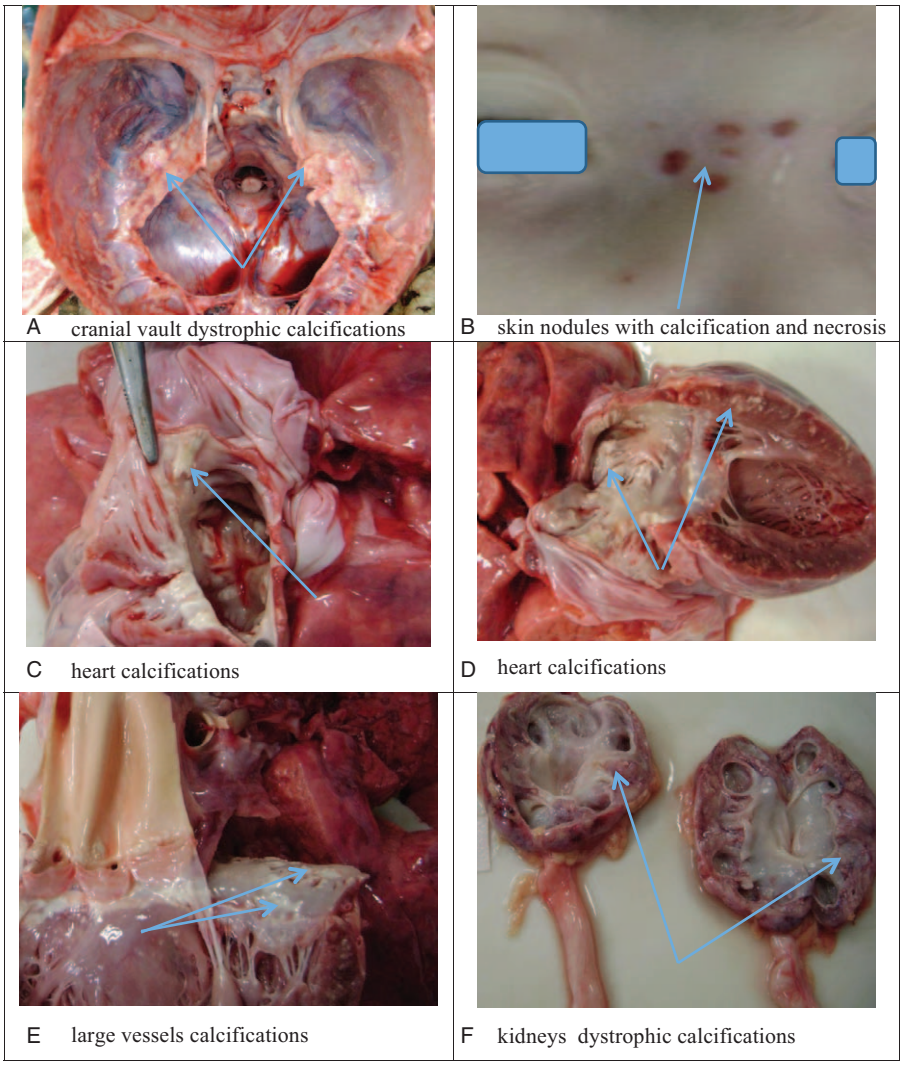

Figure 1. Dystrophic calcifications.

The serum chemistry revealed: blood urea nitrogen (BUN) of 177 mg/dL, creatinine of 5.84 mg/dL; normal electrolytes; serum albumin of 2.1 mg/dL; normal liver enzymes and cholesterol 222 mg/dL (normal 100–200 mg/dL); calcium 11.71 mg/dL, phosphorus 10.98 mg/dL (calcium–phosphorus product corrected for low albumin = 128.57 mg^2/dL^2); magnesium 1.6 mg/dL; intact PTH 765 pg/mL (n = 7–53 pm/mL). The hemoglobin was 8.9 g/dL, WBC 10.550/mm^3 and platelets 421.000/mm^3. Other tests that were done included antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), mycoplasma antibodies, and rheumatoid factor, which were all negative. Serum complements(C) C3 and C4, hepatitis serology, creatine phosphokinase (CPK), and serum immunoglobulins (except IgE which was raised) were all normal. Doppler ultrasound examinations of the superficial and deep veins of all the extremities were done and were normal, but echocardiography showed congestive heart failure with global hypokinesia, intramuscular calcifications, decreased ejection fraction (53%) and shortening fraction (27%). The chest radiograph revealed bilateral interstitial and alveolar infiltration, with peripheral disposition and cotton-wool like distribution that did not improve following ultrafiltration.

Apart from the ESRD, the provisional diagnosis for this moment was bronchopneumonia, respiratory and cardiac failure.

His pulmonary function rapidly deteriorated within 50 minutes from the moment of hospital admission, up to severe hypoxemia (PaO_2 74%), seizures and cardio-respiratory arrest, despite the initiation of intensive care measures: oxygen therapy in continuous positive airway pressure system, tonic-cardiac medication (dopamine and dobutamine), anticonvulsant medications (diazepam), and cerebral antiedematous (dexamethasone).

Post-mortem examination revealed: diffuse calcifications in the skin, skull, brain (cerebellar tentorium and dura mater), lungs and heart (subendocardial, within the myocardium and large vessels walls). Both kidneys had severe hydronephrosis with bilateral renal cortical atrophy and calcifications in the remaining renal parenchyma (Fig. 1). The histopathological examination with *hematoxylin eosin* staining, confirmed the microscopic diffuse calcifications in the skin, brain, heart, lung, kidney, stomach, and pancreas (Fig. 2). All these are consistent with the diagnostic of calcific uremic arteriolopathy.

3. Discussion

Calcific uremic arteriolopathy (CUA), previously known as calciphylaxis, has been reported to occur in 1% to 5% of adult patients with ESRD and has a mortality rate of more than 80%.[1–3] Although calciphylaxis predominantly affects patients with chronic kidney failure and secondary hyperparathyroidism, it is not limited to this group, but also occurs in patients with normal kidney function and those with earlier stages of chronic kidney disease (nonuremic calciphylaxis).[4,5] Occasionally, it may occur before the initiation of the renal replacement treatment, or in individuals with no history of chronic renal impairment. It has also been discovered in patients with renal allograft transplantation who are noncompliant with diet, medication and /or dialysis instructions.[4]

It is considered a life-threatening small-vessel vasculopathy characterized by intimal proliferation, endovascular fibrosis, and medial wall calcification, which result in ischemia and painful necrosis most commonly in the skin and subcutaneous tissues.[3] It was considered that the ischemic necrosis evolve in a rapidly progressive manner, covering large areas of the skin and muscle due to extensive vascular calcifications.[2] These areas may become ulcerated and infected, sometimes resulting in limb amputation.[6]

Metastatic calcinosis subsequent to renal insufficiency was first described by Virchow.[7] Although soft tissue calcification is a recognized complication of uremia in adult patients treated by dialysis (occurring in up to 40% to 76% of adults on maintenance dialysis), it has been considered as rare in pediatric renal patients.[8] The first pediatric CUA case was reported in 1898, by Bryant and White who described a 6-month-old boy with severe calcification of he large arteries and occlusion of peripheral arteries and arterioles associated with hydronephrosis, which led to gangrene of the right foot with a lethal outcome.[9]

It occurs rarely in children, where the reported incidence is 3.5 new cases/1000 patients/year in chronic hemodialysed pediatric patients.[10] An increased incidence was found in boys with chronic renal disease and secondary hyperparathyroidism, with acral necrosis (tip of the fingers or toes). This was associated with a poor prognosis.[11]

Hyperphosphatemia and concomitant calcium–phosphorus product are the strongest risk factors for the development of CUA. Other risk factors currently cited and also occurring in our case study are: ESRD, secondary hyperparathyroidism with increased parathyroid hormone, Caucasian ethnicity, hypoalbuminemia (malnutrition and weight loss), elevated alkaline phosphatase, and use of calcium phosphate binders.[1]

Calcifying nodules at all anatomic locations are usual manifestations of CUA. The nodules could be single or multiple, developing suddenly and progressing rapidly, more frequently located on the lower limbs and less on the upper ones or thorax, lower abdomen, or buttocks.[12] The proximal lesions have a poorer prognosis (shoulders, trunk, buttocks, and thighs), mainly because of the greater amount of necrotic and infected tissue. Distal lesions can involve the calves, forearms, acral sites, genitalia and, rarely, the face. Cutaneous lesions may be preceded or accompanied by severe pain. Initially it appears as nonspecific purple spots or erythematous papules/plaques/nodules, and then it acquire a purple star-shaped appearance followed by central necrosis. Ulcerations and sepsis may occur and contribute to increased mortality rate.[5] In our case, the subcutaneous lesions appeared few months before the dry cough, first presenting as small purple spot in the facial area. Interesting to note that the cutaneous involvement in our patient was not the most important one, but the indurated nodules without skin necrosis but with deep pain. Although extended in a systemic manner, we appreciate that the pulmonary lesions were the most severe ultimately resulting in death.

Apart from cutaneous manifestations, vascular calcifications in the skeletal muscle, brain, lungs, intestine, eyes, and mesentery have been reported.[13–19] In most cases, calcifications affect the middle layer of the arterial vessels, but damage to the intima has also been reported.[20,18] Our case presented an unusual, diffuse, and extensive calcifying uremic arteriolopathy syndrome with diffuse calcifications in the dermis, brain, thymus, heart, lung, kidney, stomach, and pancreas. From all these locations, pulmonary calcification is one of the most severe complications in patients on dialysis. Furthermore, the clinical and radiographic manifestations of this lesion may be mistakenly diagnosed as pulmonary oedema or pneumonia. Pulmonary calcification, when extensive, can be the cause of death in uremic patients.[19] We appreciate that this was also the case in this current case study. Our patient developed rapidly progressive respiratory failure. Multiple calcifications in the lungs and skin have been

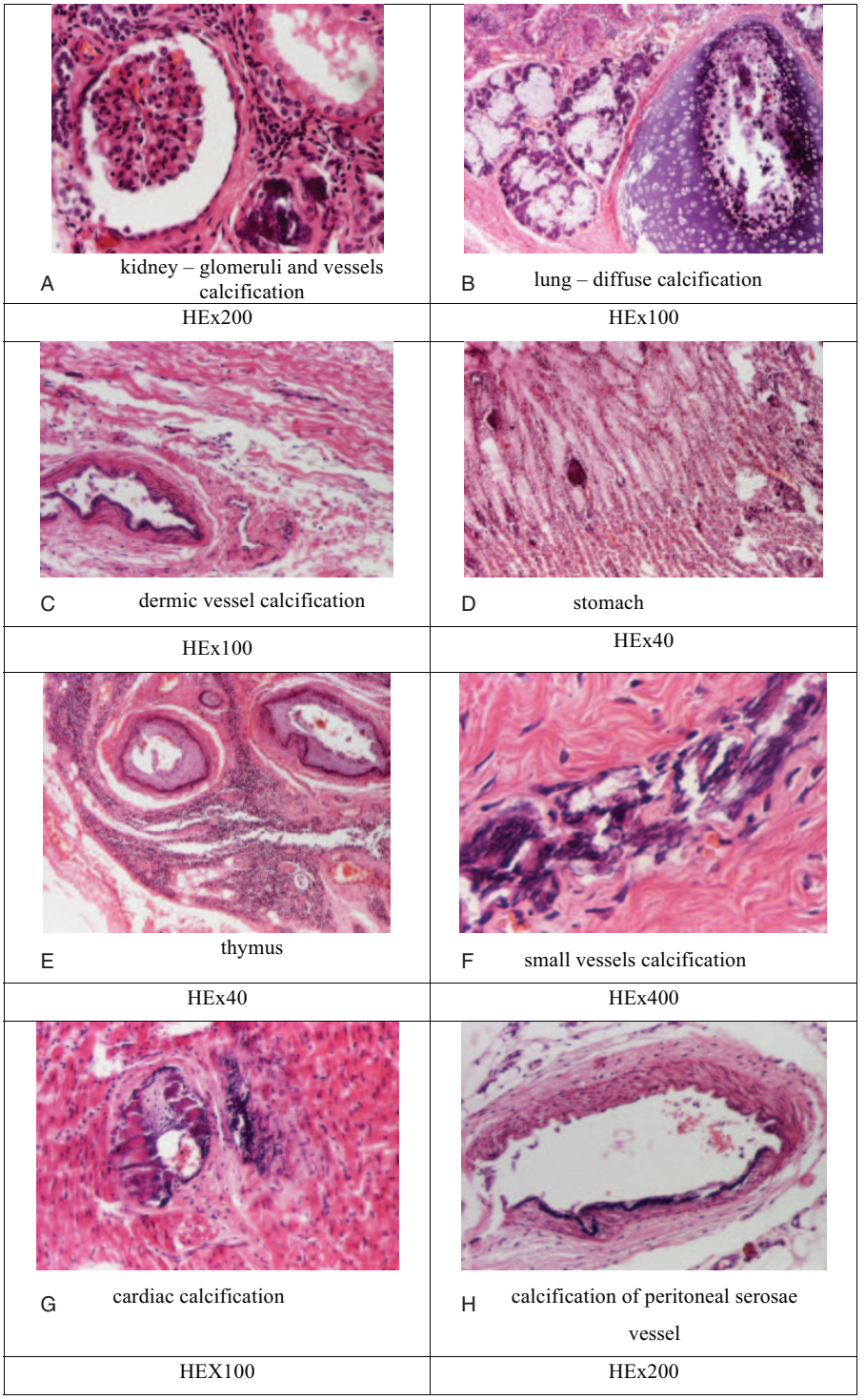

Figure 2. Calcifications—microscopic aspects (hematoxilin eosin stain).

reported by Zouboulis et al,[21] who described a 6-year-old boy undergoing peritoneal dialysis for chronic renal failure due to bilateral renal hypoplasia. Pulmonary calcinosis can be responsible even for sudden death, as it has been reported by Milliner et al[22] in an adolescent following renal transplantation. The same author has reviewed 120 pediatric patients with uremia, on dialysis or following renal transplantation who died. During these autopsies soft tissue calcifications in 72 cases, out of which 29 had pulmonary calcinosis were discovered.[23]

According to Arrestier et al,[24] the prognosis of skin calciphylaxis has improved considerably since the introduction of sodium thiosulfate (STS). However it remains unclear whether this therapy is effective against visceral lesions due to calciphylaxis, and whether authorized drug for children with CUA is available.[24] One specific issue in our case was an ethical one – related to family refusal to change the phosphate chelation treatment. We tried to introduce lanthanum carbonate in a phase III study but his parents refused. Interestingly, the same sort of

non-compliance of such treatment in children, have been reported by Toprak in an 8-year-old girl under peritoneal dialysis program for end stage renal failure due to reflux nephropathy,[25] who developed secondary hyperparathyroidism due to family non-compliance to calcitriol and phosphorus chelation therapy. Calciphylaxis manifested rapidly with multiple calcifications, including in the lungs. A parathyroidectomy did not stop the progression of the disease, and the child died suddenly during sleep. Therefore, when confronted with parental refusal and a difficult informed consent process, the pediatric management of a case might be seriously damaged.[26]

4. Conclusions

CUA is an under recognized, understudied, and undertreated rare cause of major morbidity and mortality in patients with chronic renal insufficiency regardless of etiology. The available, though heterogenous, case reports on this topic suggest an increased incidence in pediatric males and adult females. The reported pediatric patients are usually already on peritoneal dialysis at the time of diagnosis. Adult treatments have not yet been applied consistently to pediatric patients with CUA, although initial results seem promising. Prophylaxis of hyperphosphatemia and secondary hyperparathyroidism, patient compliance with doctor recommendations, and early diagnosis of calciphylaxis are believed to improve survival in these cases. Calciphylaxis remains a subject of relevance for current medical research, because the pathogenesis is not yet clarified and data on diagnosis and therapeutic approach are still under debate.

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All authors approved the final manuscript and agree to be accountable for all aspects of the work.

This original study was performed in accordance with Declaration of Helsinki (the latest revision) and approved by the local hospital ethics committee. Informed consent was obtained from the parents of reported pediatric patient.

All the data presented can be available upon request.

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