

Endocarditis and Calcific Uremic Arteriopathy: Is it a Coincidence or an Association? Case Report

Endokardit ve Kalsifik Üremik Arteriopatı: Tesadüf mü Yoksa Birlitelik mi? Olgu Sunumu

ABSTRACT

The uncommon complications regarding CKD tend to increase in clinical setting because of the chronic kidney disease (CKD) population has been expanding every passing day. Perhaps the most important one of these is calcific uremic arteriopathy (CUA, calciphylaxis). Calcific uremic arteriopathy is a clinical syndrome which includes systemic calcification of the small vessels, causes to ischemia, subcutaneous necrosis and it has high mortality and morbidity rates (1,2). There is a large body of data in literature about CUA although very little for its cardiac involvement. Herein we presented a case of calcific endocarditis with CUA and the review of the literature. According to our observation, parathyroidectomy was effective to provide clinical and radiological improvement in the presented case. The clinician should consider adding parathyroidectomy to conventional strategies immediately if the risk of such uncontrolled hyperparathyroidism is present.

KEY WORDS: Calcific uremic arteriopathy, Calciphylaxis, Chronic kidney disease, Endocarditis, Parathyroidectomy

ÖZ

Kronik böbrek hastalığı(KBH)'ndan etkilenen popülasyonun her geçen gün büyümesi nedeniyle KBH ile ilişkili sık olmayan komplikasyonlar klinik paratiktte artma eğilimindedir. Bu komplikasyonların belki de en önemlisi kalsifik üremik arteriopatı (KÜA, Kalsiflaksi)'dir. Kalsifik üremik arteriopatı küçük damarların kalsifikasyonunu, iskemiye, ciltaltı dokunun nekrozunu içeren ve yüksek morbidite/mortalite oranlarına sahip klinik bir sendromdur (1,2). Literatürde KÜA hakkında birçok veri olmasına rağmen KÜA'ye bağlı kardiyak tutulum ile ilgili veri çok azdır. Biz burada KÜA ile birlikte olan bir endokardit vakası ve literatür derlemesini sunduk. Gözlemlerimize göre sunulan vakada paratroidektomi etkin klinik ve radyolojik düzelme sağladı. Klinisyen kontrolsüz hiperparatirodizm gibi risk faktörü varsa geleneksel tedavi stratejilerine ek olarak gecikmeden paratroidektomi operasyonunu düşünmelidir.

ANAHTAR SÖZCÜKLER: Kalsifik üremik arteriopatı, Kalsiflaksi, Kronik böbrek hastalığı, Endokardit, Paratroidektomi

INTRODUCTION

Calcific uremic arteriopathy (CUA, calciphylaxis) is a rare complication of chronic kidney disease and has high morbidity and mortality rates. It is a clinical syndrome that includes systemic calcification of the small vessels (arterioles and venules), causing ischemia and subcutaneous necrosis (1, 2). Endocarditis may develop in this uncommon entity but it is very rare. Herein we presented a case of sterile calcific endocar-

ditis associated with CUA and the review of the literature.

CASE REPORT

A 32-year-old man had end-stage renal disease (ESRD) caused by chronic glomerulonephritis. He had rejected allograft and had been receiving hemodialysis (HD) treatment three times a week for twelve years. He was referred to our nephrology clinic with acral painful cutaneous lesions. The patient stated that the cutaneous lesions

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were emerging suddenly on the tips of his fingers and toes and then transforming into black lesions in two or three days. Physical examination revealed body mass index: 32 kg/m², body temperature: 36.5 Celsius, cardiac rate: 84/min, respiration rate: 16/min, and arterial blood pressure: 140/95 mmHg; a cardiac systolic murmur, cutaneous necrotic lesions on the tips of the fingers and toes (Figure 1D,E) and linear cutaneous lesions as a result of pruritus at different body sites. Laboratory test revealed white blood cell count, 17100/uL; C-reactive protein: 1.87 mg/dL (0-0.34 mg/dL) calcium: 9.4 mg/dL (8.6-10 mg/dL); phosphorus: 7.6 mg/dL (2.4-5.1 mg/dL); albumin: 3.8 g/dL (3.2-4.8 g/dL) alkaline phosphatase: 361 U/L (45-129 U/L); and intact parathyroid hormone: 1487.3 pg/mL (15-68.3 pg/mL). Hyperthyroidism was also detected on laboratory tests. Serum anti-nuclear antibody, C3, and C4 levels were studied for the differential diagnosis and all were normal. Doppler ultrasonography showed normal flow type in extremity arteries. Echocardiography for possible cardiac etiologies was performed and showed a 11x11 mm calcific mass on the posterior mitral valve (PMV) and a 15x10 mm suspected mass or vegetation on the left ventricle outlet, together with type 1 diastolic dysfunction and concentric ventricular hypertrophy. Trans-esophageal echocardiography detected that both were

nodular calcific lesions with 5x5 mm mobile hyper-echogenic formations on PMV. Peripheral blood samples were obtained for culture. Serum procalcitonin level was 1.26 ng/mL (0-0.05 ng/mL). For the suspicion of bacterial endocarditis, empiric treatment of sulbactam/ampiciline 2x2 gr was started and had continued for two weeks although all of the cultures were negative. Fundoscopic evaluation was performed for Roth spots but was normal. Contrast-free thorax CT showed mitral valve calcification. Positron emulsion tomography (PET/CT) with NaF (sodium fluoride) showed positive uptake in the calcific valvular areas only. The Trucut cutaneous biopsy from the necrotic lesion showed dermal calcification with von kossa staining (Figure 1C). Infective endocarditis was ruled out after these findings and the diagnosis of CUA with cardiac/valvular calciphylaxis was made. Parathyroid syntigraphy with 20 mCi Tc-99m MIBI showed an adenoma. Parathyroidectomy with total thyroidectomy (diffuse multinodular goiter was detected on thyroid scintigraphy) was performed urgently. The serum parathyroid hormone level decreased to 3 pg/mL and hungry bone syndrome was observed in the follow-up period after the operation and treated with appropriate intravenous vitamin D3/calcium supplementation. L-thyroxine treatment was started for hypothyroidism. After the operation, the cutaneous lesions

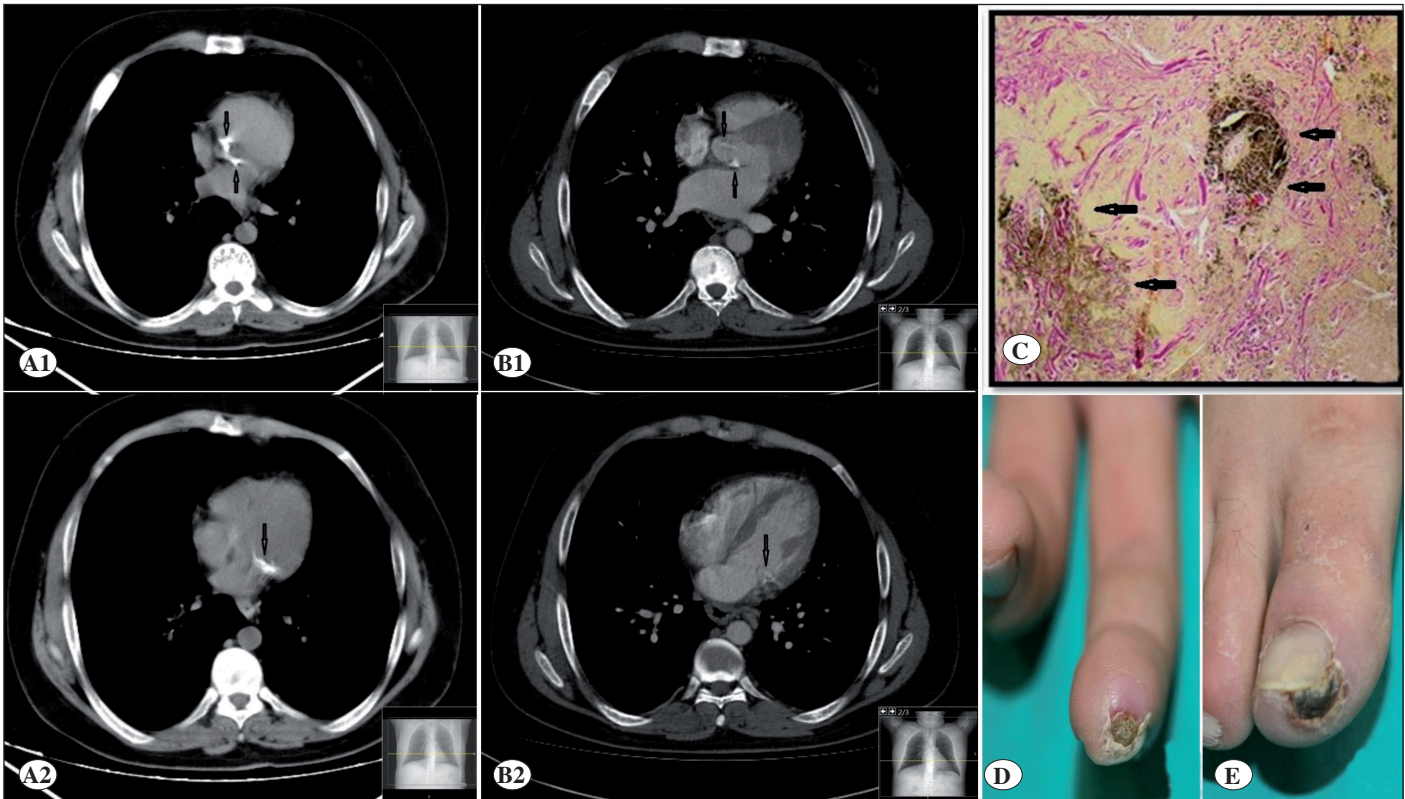


Figure 1: A1-2) Thorax CT on admission (without iv. contrast medium); The areas of the calcification on the valves (arrows) B1-2) Thorax CT after the six months (with iv. contrast medium); The decreasing of valvular calcification significantly (arrows) C) Von Kossa stained slides confirmed calcification in dermis (arrows) D-E) The clinical appearance of the patient.

completely healed in three weeks and no new lesions appeared. Reflux esophagitis refractory to proton pump inhibitors developed at the sixth month of follow-up and esophago-gastro-duodenoscopy was performed. The lesion with malignant features was evaluated and a biopsy performed. Thorax-upper-abdomen CT with contrast medium was also obtained for a possible malignant process. The calcific masses on the mitral valve were significantly smaller on the second CT when compared to the preoperative one (Figure 1 A1,2; B1,2).

DISCUSSION

Vascular and Valvular Calcification in CKD Patients

There are four known types of CV calcifications in CKD patients; arterial intima layer (atherosclerotic plaque) calcification, arterial media layer calcification (Monckeberg's disease), cardiac valvular calcification and CUA or calciphylaxis (2, 3). Atherosclerotic plaque and intimal calcification are related to classical Framingham risk factors including advancing age, hypertension, dyslipidemia and smoking. This process is usually patchy and affects the intimal arterial wall discontinuously. The macrophages and vascular smooth muscle cells (VSMCs) can be seen in atherosclerotic plaque (3, 4). Arterial medial calcification, also known as Mönckeberg's disease, has a close association with CKD and diabetes. A sheet-like calcification with concentric thickening in the arterial media layer and intimal involvement was not seen in the affected areas (4). These two processes have different clinical consequences in CKD patients. The former can cause ischemic heart disease, while the last one can lead to systolic hypertension, left ventricular hypertrophy (LVH) and vascular stiffness (3, 4). The incidence of the third one, valvular calcification, is very high in dialysis patients when compared to the normal population (5, 6). In one study, the rate of calcification was 59% on the mitral valve and 55% on the aortic valve in dialysis patients (5). The incidence of both mitral and aortic valve calcification was 49% in ESRD patients in a more recent study (6). Aortic valve calcification can be a cause of valvular stenosis, LVH with or without dysfunction whereas mitral valve calcification can lead valvular insufficiency or stenosis, arrhythmias, endocarditis, thrombo-embolic events, stroke and cardiac failure. The endothelial cells, VSMCs and valve interstitial cells are the key cells in the pathogenesis of these three calcification types in CKD (3, 4, 7).

The mechanism of the fourth one, calciphylaxis or CUA, is not clear and the pathogenesis is unlikely to be similar with these three forms of calcification discussed above. It is an uncommon syndrome although the others have a very high incidence rate in the dialysis population. It especially involves capillaries, venules, arterioles and small (average size 100 µm) arteries while others usually affect medium and large size arteries (8). The histology contains not only medial calcification but also intimal proliferation, endovascular fibrosis, thrombosis of the capillaries. Finally, it can develop in the patients without CKD

(8, 9). All these findings suggest that this is a more complex entity than simple vascular calcification.

Differential Diagnosis of CUA

Although the cutaneous lesions classically develop on body sites such as the abdomen, buttocks, and thigh, digital ulcers with necrosis can also be detected on physical examination (7% of cases) (10). If these acral findings exist, the diagnosis may be confused with infective endocarditis especially when valvular involvement is detected on echocardiography. Both FDG and NaF (sodium fluoride) PET/CT imaging can be used to obtain advanced information about the valvular lesions (11, 12). In our case, we used NaF PET/CT because of severe calcification on CT. It is a powerful technique to differentiate whether the lesion is due to sole calcification or secondary to other inflammation causes (12). It showed NaF (sodium fluoride) uptakes on the valves with calcified masses. This finding indicated that the calcific process is responsible in this case. Immunological tests and the cutaneous biopsy were also performed to differentiate other possible diagnoses including etc. rheumatologic disease, cryoglobulinemia, cholesterol embolization and vasculitis. There were no positive results on immunologic analysis. The epidermis was ulcerated and the dermis was filled with basophilic material suggestive of calcium deposition on cutaneous biopsy. Histochemical studies with Von Kossa that were performed based on the clinical suspicion of CUA exhibited deposits of calcium in the dermis (Figure 1C). The diagnosis of CUA was made after these findings and it was thought the valvular lesion could be secondary to CUA.

CUA in CKD Patients

The intimal proliferation and endovascular fibrosis with or without medial vessel calcification cause thrombosis formation within the small size of the capillaries that include both arterioles and venules in CUA (8, 13). The decreased blood flow in dermal/hypodermal arterioles leads to the the clinical manifestations. The cutaneous lesions classically develop on body sites that contain large amounts of adipose tissue, including the abdomen, buttocks, and thigh (13). The one-year mortality rate is %55 in CUA patients with CKD. The majority of deaths is caused by infections in CUA patients. This complication is more frequent in the patients who have proximal lesions rather than distal ones (14). The retrospective evaluation of 172 patients suffering from CUA showed that the lesions were on the legs, abdomen, buttocks and distal sites (hand and foot) in 60, 23, 9 and 7 percents of cases, respectively (10). The presented case had digital lesions and according to the other study these patients with digital lesions have a somewhat better prognosis compared to patients who have classical lesions (10, 15).

Sterile calcific endocarditis and systemic CUA association is very rare. Indeed the term of "sterile calcific endocarditis" is difficult to establish because of possible false negative results in some cases of infective involvement of the valves. In a

study, approximately 14% of infective endocarditis cases were misdiagnosed even when repeated cultures of blood samples were performed (16). In light of these data, it is unclear whether endocarditis is a coincidence or secondary to CUA although we did not detect any infective agent in our case. However, this association of CUA with involvement of the valves or other sites of the heart has very high mortality rate in literature. The 45-year-old male was the first case with CUA and endocarditis presented by Alam et al. (17). There are no data on whether the endocarditis is infective or secondary to CUA but this patient died after two weeks. The diagnosis was made with the post-mortem histological evaluation that demonstrated systemic CUA with large areas of calcification present within the media of the coronary vessels and myocardium. He had both distal and proximal cutaneous lesions. The other case was 36 year-old female who had calcific myocardium without valvular calcification, as presented by Tom and Talreja (18). There is neither a follow-up period nor available data regarding the patient after the diagnosis. The third case was a female, 30 year-old CKD patient who had undergone renal transplantation with hyperparathyroidism. She died because of progressive heart failure after transplantation. White myocardium was detected with computed tomography. The autopsy revealed a 590 gr heart with calcific myocardium (19). For now this is a mystery how CUA influences the heart and which parameters determine which site of the heart will be involved. We believe that our case was affected by CUA and the valves were involved. He has been followed in good health for six months after all cutaneous lesions healed.

The risk factors of CUA that have been described in the literature are longer time of HD exposure, female sex, obesity, existence of hypercoagulopathy (protein C, S deficiency and antiphospholipid syndrome), hyperphosphatemia, hyperparathyroidism; medications such as warfarin, calcium-based phosphate binders, i.v. iron therapy, vitamin D analogs, and systemic glucocorticoids, and hypoalbuminemia (14, 20-23). The dialysis exposure and longer duration on dialysis treatment are important facilitators for CUA although CUA can develop in non-CKD patients (9). The increasing Ca product P, alkaline phosphatase and P levels due to CKD have been described as the risk factors for CUA in ESRD patients (24). These patients also have lower fetuin-A levels than the normal population. Fetuin-A is a well known anti-inflammatory substance and an inhibitor glycoprotein on vascular calcification (23). In addition, Janigan DT et al. have showed that obesity can also be an independent risk factor for CUA (22). Their hypothesis was that the increased adipose tissue in obesity causes expansion of the subcutaneous compartment. This prolonged stretch tension on septa and arterioles with coexisting edema lead to CUA (22). Our patient had twelve years of HD exposure, obesity, hyperphosphatemia and hyperparathyroidism. Despite the multi-factorial nature of disease, we thought hyperparathyroidism was the overwhelming mechanism in our patient after the treatment course.

Treatment Strategies of CUA

The treatment of CUA is not well established in CKD patients. However there are some described strategies in literature such as aggressive wound care (if necessary debridement may be performed), avoidance of subcutaneous and muscular injections, oxygen therapy (10-15 L, two hours/day or 2.5 atm for 90 minutes/day), maintaining calcium, phosphorus, CaxP ($<55 \text{ mg}^2/\text{dL}^2$) and PTH levels ($>300 \text{ pg/dL}$, cinacalcet or surgery) in the target range, intravenous sodium thiosulfate (25 gr, diluted in 100 mL of physiological saline solution and administered over 30 to 60 minutes, three times a week until complete wounds healing is achieved), increased HD dose using low dialysate calcium (1-1.5 mmol/L) and stopping or switching the drugs that affect the calcium-phosphorus metabolism (14, 21, 25-30). Vitamin K, denosumab, vitamin D receptor agonists, teriparatide, avoiding zinc deficiency and bisphosphonates may be other potential alternatives although more relevant data are required for routine use (7).

In our patient, the hemodialysis (dialysate calcium 1.25 mmol/L) dose was increased to 16 hours weekly to keep calcium and phosphorus levels in the target range. Oral phosphorus binding agent therapy was switched to sevelamer and continued with cinacalcet therapy at a dose of 90 mg/day. Oxygen treatment was applied at 10 L/min approximately two hours daily. The effectiveness of parathyroidectomy is controversial according to the literature. Some of the studies and case reports support the beneficial effects but others do not (14, 21, 25, 31, 32). The significant regression of the calcification in the six months after the operation indicates that hyperparathyroidism could have played a major role in systemic CUA and valvular calcification in this case. Similarly, Arch-Ferrer et al. found that patients treated with parathyroid surgery had a higher median overall survival than patients were treated conservatively (80 versus 35 months) in their retrospective study (32). The main risk factor, hyperparathyroidism, was treated with total parathyroidectomy in our case.

CONCLUSIONS

Calcific sterile endocarditis associated with CUA is an uncommon severe disease. There are many described strategies for CUA treatment but none in this condition on literature. The presented case is the second case in the literature as a CUA case associated with valvular calcification/endocarditis and also the first one who is living in good health for six months after the diagnosis. We believe the clinician should consider adding parathyroidectomy to conventional strategies immediately if a risk of uncontrolled hyperparathyroidism is present in cases of endocarditis associated with CUA.

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