Case Report

Calcific Uremic Arteriolopathy- An Atherosclerotic Masquerade

Thajudeen B, William P and Bijin B*
Department of Medicine, University of Arizona, USA

Abstract

Calcific uremic arteriolopathy is a poorly understood disease causing vascular calcification and skin necrosis in end stage renal disease patients. Atherosclerotic peripheral vascular disease is another common disease seen in patients with end stage renal disease. Diagnosis of calcific uremic arteriolopathy could be missed in presence of atherosclerotic peripheral vascular disease. Here we describe the case of a calcific uremic arteriolopathy masqueraded by atherosclerotic peripheral vascular disease. A 65 year old Hispanic male with end stage renal disease on peritoneal dialysis and peripheral vascular disease presented with excruciating painful lesions involving extremities. Despite intervention for peripheral vascular disease he had progression of skin lesions. His medications included calcium acetate, calcitriol and history of use of warfarin 6 months back. Physical examination was significant for gangrene of fingers and toes and multiple ulcers involving hands, forearms, legs, dorsum of foot and heel. Laboratory tests showed hypercalcemia, hyperphosphatemia and hyperparathyroidism. Due to predisposing factors and distribution of ulcers, possibility of calcific uremic arteriolopathy was raised. A skin biopsy showed findings consistent with calcific uremic arteriolopathy. In addition to discontinuation of calcium based binders and calcitriol, hemodialysis six times a week, intravenous sodium thiosulphate and continuous oxygen therapy were initiated. A well-defined natural course of the disease has still not been established and no randomized controlled trial is available to guide the treatment. Just as risk stratification has been emphasized in atherosclerosis, simultaneous reduction of risk factors like bone mineral metabolism, sensitizing and challenging agents in calcific uremic arteriolopathy is essential.

ABBREVIATIONS

CUA: Calcific Uremic Arteriolopathy; ESRD: End Stage Renal Disease; CKD: Chronic Kidney Disease; PVD: Peripheral Vascular Disease; HBO: Hyperbaric Oxygen

INTRODUCTION

Calcific Uremic Arteriolopathy (CUA) is a poorly understood disease causing vascular calcification and skin necrosis and occurs most commonly in patients with late stage Chronic Kidney Disease (CKD), end stage renal disease (ESRD), or after transplantation [1]. The mortality associated with this condition is in the range 60-80%, mostly from sepsis and cardiovascular events [2]. It is thought to involve an imbalance between inducers and inhibitors of calcification of the vascular wall. The estimated incidence of CUA is approximately 4% in hemodialysis patients [3]. Atherosclerotic peripheral vascular disease (PVD) is another common entity seen in ESRD patients. Diagnosis of calcific uremic arteriolopathy could be missed in presence of atherosclerotic PVD. Here we report the case of CUA masqueraded by atherosclerotic PVD.

CASE PRESENTATION

A 65 year old Hispanic male presented to our hospital with excruciating painful lesions involving the left upper extremity. He had gangrenous lesions involving distal aspects of upper and lower extremities (mainly fingers and toes) for past 2 years and was diagnosed with atherosclerotic peripheral vascular disease one year ago for which he underwent endovascular intervention. Despite the intervention there was progression of the skin lesions. Over the past several months he noticed new skin lesions which started as small painful nodules which subsequently became much larger, black, ulcerated lesions spreading to hands, forearms, foot and legs. He also had a history of deep vein thrombosis one year ago which was treated with warfarin for 6 months. Significant other past medical history included poorly controlled type 2 diabetes mellitus and hypertension. Additional dialysis related problems included anemia treated with erythropoietin, secondary hyperparathyroidism treated with calcitriol and hyperphosphatemia treated with calcium acetate. Physical exam showed dry gangrene of fingers and toes, multiple ulcers covered with dark eschar involving hands, forearms, legs, dorsum of foot and heel. All peripheral pulses were feeble in both upper and lower extremities. Relevant laboratory tests
at admission included hemoglobin 9.2 gm/dl, calcium 10.6 mg/dl, phosphorus 6.5 mg/dl, parathyroid hormone 400 pg/ml and albumin 2.2 gm/dl. A computed tomographic angiography of the left upper extremity showed diffuse atherosclerotic calcifications as well as stenosis of brachial, ulnar and radial arteries. The patient underwent left ulnar artery exploration with patch angioplasty with left basilic vein, left ulnar artery percutaneous transluminal angioplasty and left distal 2nd, 3rd, 5th finger angioplasty (performed by vascular surgery). At the onset all the skin lesions were presumed to be due to atherosclerotic disease. However due to predisposing factors and proximal distribution of some of the ulcers, possibility of coexisting CUA was also raised. A biopsy of skin over affected area on upper extremity showed gangrenous necrosis of soft tissue with calcification of the subcutaneous arterioles consistent with CUA (Figure 1). Calcium supplements and calcitriol were stopped. Peritoneal dialysis was replaced by six times a week hemodialysis using low calcium bath. In addition to use of non-calcium based phosphate binders treatment with thrice a week intravenous sodium thiosulphate was also started. Wound care and continuous oxygen therapy was initiated as well with some improvement in the skin lesions. Patient eventually died of sepsis.

**DISCUSSION**

Co-existence of CUA and peripheral vascular disease is not uncommon in ESRD patients. A high index of suspicion is required for diagnosis of CUA in the back ground of underlying atherosclerotic peripheral vascular disease (PVD). The lesions of CUA usually start as livedo reticularis, progressing to violaceous, painful, plaque or subcutaneous nodules and eventual development of ischemic/necrotic ulcers [1]. Areas commonly affected are the lower limbs and those with thick adipose tissue, such as the breasts, abdomen and gluteal region [4]. Besides the skin, other organs and systems can be involved such as lung, eyes, heart, kidneys, skeletal muscle, tongue, pancreas and gastrointestinal tract [4]. These ulcers are usually located more proximally on the extremity [5]. Histopathologic features of CUA include calcification of both the medial and intimal layers of small and medium size vessels in a circumferential distribution [5]. Additionally there will be intimal hyperplasia with partial obliteration of the vessel lumen and fibrin thrombi [5]. Presence of preserved peripheral pulses, subcutaneous nodules, radiological studies showing vascular calcification, calcification of small and medium sized venules as well as arterioles on histopathology and symptoms of extreme pain favor a diagnosis of calciphylaxis wound. Occasionally the lesions of CUA can be seen in hands and fingers mimicking peripheral vascular disease [6].

The symptoms of peripheral vascular disease include claudication characteristically involving lower back, buttocks, thighs and legs depending on the site of occlusion [7]. In males it might be associated with impotence as well. The skin lesions of peripheral vascular disease are usually painful, nonhealing, distal ulcers seen mainly in the legs and feet [8]. They are associated with decreased blood flow to the extremities manifested as diminished pulses. Atrophic skin, loss of hair and cool extremities are other features. In advanced disease they have pain at rest as well. The diagnosis can be established by physical examination, leg pressure measurements (ankle-brachial index), duplex ultrasonography, computed tomographic angiography, magnetic resonance angiography and conventional angiogram [8]. Histopathology of atherosclerosis is characterized by accumulation of cholesterol, infiltration of macrophages, proliferation of smooth muscle cells (SMC), accumulation of connective tissue components and formation of thrombus [7]. Occasionally calcification can also be seen mainly in the form of intimal calcification [9]. Atherosclerotic vascular disease usually affects medium to large sized blood vessels. (Differences in the signs and symptoms between CUA and atherosclerotic PVD are represented in table 1).

Secondary hyperparathyroidism, persistent elevation of serum phosphorus, and consequent increased calcium-phosphorus product has been postulated to play a role in vascular calcification of CUA whereas hyperlipidemic states, diabetes mellitus, smoking, hyperhomocysteinemia and hypertension are the major risk factors for atheroclerotic PVD [2]. Other major risk factors for CUA include prolonged duration of dialysis, white race, younger age, female gender, insulin dependent diabetes, low serum albumin, elevated serum alkaline phosphatase, protein C and/or S deficiency, parenteral iron, use of immunosuppression including corticosteroids, exposure to warfarin, metabolic alkalosis post hemodialysis, local trauma, obesity (body mass index of 30 or above) and liver disease [2, 10]. In this case, use of warfarin might have been the predisposing factor for development of calciphylaxis. Warfarin likely promotes the development of CUA by reducing functional protein C levels and blocking vitamin K-dependent carboxylation of the matrix GLA protein, which is a local inhibitor of vascular calcification [11].

The pathogenesis of CUA is related to the increased expression of osteopontin and bone morphogenic protein in the vascular smooth muscle cells and dermal cells respectively [12]. Additionally these vascular smooth muscle cells transform into (osteogenic) osteoblast like cells (via expression of core-binding factor-1) and express bone-related proteins such as osteocalcin, bone sialoprotein, type 1 collagen [12]. Pathogenesis of atherosclerosis PVD involves endothelial dysfunction, lipid
accumulation, immune response, vascular smooth muscle cell migration, matrix turnover, and calcification [9]. The calcification associated with these lesions also involve increased expression of osteopontin (similar to CUA) and bone morphogenetic protein promoted by inflammatory cytokines, oxidized lipids, and monocyte-macrophage products [9]. The overlap in the pathogenesis makes us wonder whether there are synergic factors involved in the onset and progression of both disease entities. It is already known that risk factors associated with CUA like hyperphosphatemia and hyperparathyroidism have association with aortic and coronary vascular calcification [9]. This is a potential area for more research.

Early recognition of calciphylaxis and institution of early and aggressive intervention with the use of multi-faceted therapeutic approaches including local wound care, aggressive dialysis regimens, phosphate lowering medications, avoidance of calcium containing medications, use of sodium thiosulphate, parathyroidectomy, hyperbaric oxygen therapy and appropriate arterial revascularization as well as risk factor modification for atherosclerosis can lead to improved wound healing and limb salvage in patients with CUA superimposed on atherosclerotic PVD [1,13]. Currently, there are no randomized prospective controlled clinical trials available showing efficacies of any treatment modalities. Some recent literature suggests intravenous sodium thiosulphate as a first-line agent, especially in absence of hyperparathyroidism. A potential mechanism of action of sodium thiosulphate is closely linked to its antioxidant, vasodilator therapeutic approaches including local wound care, aggressive dialysis regimens, phosphate lowering medications, avoidance of calcium containing medications, use of sodium thiosulphate, parathyroidectomy, hyperbaric oxygen therapy and appropriate arterial revascularization as well as risk factor modification for atherosclerosis can lead to improved wound healing and limb salvage in patients with CUA superimposed on atherosclerotic PVD [1,13]. Currently, there are no randomized prospective controlled clinical trials available showing efficacies of any treatment modalities. Some recent literature suggests intravenous sodium thiosulphate as a first-line agent, especially in absence of hyperparathyroidism. A potential mechanism of action of sodium thiosulphate is closely linked to its antioxidant, vasodilator properties [14]. Hyperbaric oxygen(HBO) is another treatment option found effective in patients with CUA. It counteracts local tissue hypoxia while improving wound healing via increased angiogenesis and fibroblast proliferation with collagen formation to promote wound healing. Additionally, HBO therapy may increase bact erical activity in infected wounds by increasing the respiratory oxidative burst from neutrophilic phagocytic NADPH oxidase [15]. Efforts must also be made to correct the plasma calcium and phosphorus concentrations in order to achieve a calcium and phosphorus content below 5.5 mg/dL and serum levels of phosphate between 2.7 mg/dL and 4.6 mg/dL Due to high mortality rate and no clear benefits of treatment once the diagnosis of CUA has been established, early initiation of palliative care with adequate pain control would be another viable treatment option for these patients.

### Table 1: Differences in the signs and symptoms between CUA and atherosclerotic PVD.

<table>
<thead>
<tr>
<th>Signs or symptoms</th>
<th>CUA</th>
<th>Atherosclerotic PVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of ulcer</td>
<td>Usually proximal part of extremities. Occasionally seen distally as well</td>
<td>Mostly distal part of extremities</td>
</tr>
<tr>
<td>Peripheral pulse</td>
<td>Preserved</td>
<td>Weak or absent</td>
</tr>
<tr>
<td>Age</td>
<td>Relatively younger age</td>
<td>Elderly</td>
</tr>
<tr>
<td>Gender</td>
<td>More common in females</td>
<td>More common in males</td>
</tr>
<tr>
<td>Risk factors</td>
<td>High phosphorus, high calcium X phosphorus product, hyperparathyroidism.</td>
<td>Smoking, diabetes, hypertension, Homocysteinemia</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Skin biopsy</td>
<td>Ankle-brachial index, angiogram</td>
</tr>
<tr>
<td>Site of calcification</td>
<td>Tunica media and intima</td>
<td>Tunica intima</td>
</tr>
<tr>
<td>Type of blood vessels</td>
<td>Small and medium size</td>
<td>Medium to large size</td>
</tr>
<tr>
<td>Treatment</td>
<td>Control of phosphorus, calcium, hyperparathyroidism, use of sodium thiosulfate, intensification of dialysis treatment</td>
<td>Risk factor modification(tobacco cessation, antiplatelet and lipid-lowering therapies), revascularization</td>
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### CONCLUSION

A high index of suspicion is essential in the diagnosis of CUA especially in the background of atherosclerotic peripheral vascular disease. Prompt recognition could result in improved outcomes in such patients in terms of both morbidity and mortality. Simultaneous intervention including reduction of risk factors for CUA and atherosclerosis should be carried out in such cases.

### CONFLICT OF INTEREST

All authors are equally involved in the preparation of this manuscript. All authors have read the manuscript and agree to its publication in this form. The contents of this paper have not been published previously in whole or part. All authors report no conflict of interest.

### REFERENCES


