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Tiago João Martins Oliveira

Calciphylaxis:
from the disease to the diseased

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Calciophylaxis: from the disease to the diseased

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Abstract

Calciophylaxis, or calcific uremic arteriolopathy, is a vascular ossification-calcification disease involving cutaneous or visceral arterioles, with ischemic damage of the surrounding tissues, usually in the setting of chronic kidney disease. Pathogenesis is still unclear and probably comprises the participation of vascular smooth muscle cells, endothelial cells and macrophages surrounded by a uremic and/or pro-calcifying environment. According to the original concept of calcific uremic arteriolopathy coined by Hans Selye, risk factors may be divided into sensitizers and challengers and their knowledge is useful in clinical practice to pre-emptively identify both uremic and non-uremic 'at risk' patients and guide treatment. Systemic calcific uremic arteriolopathy is a rarity. Cutaneous calcific uremic arteriolopathy is more frequent and clinically presents as a first phase of cutaneous hardening and erythema, followed by a second phase of ulcerations and scars; these two phases are probably associated with the initial development of arteriolar lesion and tissue ischemic damage, respectively. Clinical history, physical examination, laboratory, histology and imaging are the main tools to exclude important differential diagnoses and obtain a definitive diagnosis. Treatment is generally unrewarding and consists of rigorous control of comorbid conditions, anti-oxidant, anti-inflammatory and antithrombotic strategies, avoidance of iatrogeny and wound and pain management. Prognosis remains poor in terms of morbidity and mortality. Efforts should be made towards a greater awareness of calcific uremic arteriolopathy, development of better therapies and improvement of clinical outcomes.

Keywords calcific uremic arteriolopathy · calciophylaxis · chronic kidney disease – mineral and bone disorders · vascular ossification-calcification · soft tissue calcification

Introduction

Chronic kidney disease (CKD) comprises a variety of homeostatic imbalances arising from a severely compromised renal function, as well as the influence of cardiometabolic comorbidities. Uremic syndrome is an umbrella term for the clinical consequences of these phenomena throughout the body. In particular, dysregulation of calcium (Ca) and phosphate (P) metabolism plays a central role in the development of

changes in bone (renal osteodystrophy) and extraosseous calcification involving vessels, extraosseous soft tissues and other structures [1].

Calcification of the vascular tree, also known as vascular ossification-calcification, is a highly prevalent complication of CKD. It is a result of multifactorial, coordinated and active osteochondrogenic processes occurring in the vessels. Chronic injurious stimuli in certain chronic diseases, namely CKD, produce an environment of metabolic toxicity in the vasculature favourable to mineralization [2, 3].

Calciphylaxis, or calcific uremic arteriolopathy (CUA), is a systemic pathology of extraosseous calcification. Usually, but not always [4], it occurs in the context of CKD and affects dermal, subcutaneous and/or visceral arterioles and soft tissues, according to histopathologic and functional studies [5, 6]. Some authors view CUA as a pure small-artery disease which should be clearly differentiated from soft tissue calcification [7], but CUA is also regarded as one of the five subtypes of *calcinosis cutis* [8].

As a middle ground between these concepts, CUA may be perceived as a vascular ossification-calcification disease with other associated phenomena in the arterioles and surrounding tissues, leading to significant ischemic damage and other dermatologic, soft tissue and/or visceral manifestations [6].

This review aims to describe the pathway from the pathophysiologic roots of the disease to the strategies used in the diagnosis and treatment of the CUA patient.

Methods

Searches were performed in the electronic PubMed database with combinations of the following words: “calciphylaxis”, “calcific uremic arteriolopathy”, “renal osteodystrophy”, “vascular calcification”, “visceral calciphylaxis” and “systemic calciphylaxis”. Related articles mentioned in the reference sections of some of the retrieved articles were also considered. Articles not written in English or without accessible full texts were excluded.

A multi-layered pathogenesis

Active vascular ossification-calcification processes in the tunica media of the arterioles are the anchor of the development of CUA [9-11]. However, they are not enough to explain the whole clinical picture, correctly establish the diagnosis or justify some of the therapeutic strategies currently used [12].

Neither a step-by-step pathogenic pathway nor the relative weight of all the factors involved are known. It is thought that CUA is a multifactorial disease ensuing from an intricate interaction of events happening in all the arteriolar layers, arteriolar lumen and surrounding skin, soft tissues, and/or visceral parenchyma. This leads to medial calcification without associated intimal calcification or vasculitic changes and one or more of the following alterations: extracellular matrix (ECM) remodelling, subintimal fibrosis, thrombus formation and tissue inflammation, calcification, ischemia and necrosis [3, 5, 13].

Figure 1 outlines some possible pathophysiological mechanisms of CUA. The main cellular protagonists are vascular smooth muscle cells (VSMCs) of the arteriolar media and endothelial cells of the arteriolar intima. Macrophages are the main cellular expression of a prominent inflammatory response observed in CUA [13]. All these cells are part of a very specific environment along serum and ECM.

Serum and ECM set the ground for CUA

Serum is the vehicle of major systemic factors strongly associated with CUA, making ECM and cellular events happen, as described below. It reflects unique characteristics and comorbidities of the CUA patient (described in “Clinical aspects”).

The balance between pro- and anti-calcification factors in the serum is particularly critical in vascular ossification-calcification diseases [14], including CUA. Raised serum Ca-P product (CaXP) and the protein fetuin-A promote and inhibit vascular ossification-calcification, respectively. In general, CaXP is increased and fetuin-A is decreased in CUA; however, in a subset of patients, CUA may occur without these changes [13, 15].

Raised CaXP may be a result of increased serum levels of Ca, P or both. It is a marker of impaired Ca and P metabolism in CKD, as well as an independent risk factor of extraskeletal calcification, strongly associated with increased mortality [16]. High CaXP was thought to trigger passive precipitation of calcium-phosphate crystals in the vessel wall [17]. However, more recent studies refute this simplistic view,

showing that, instead of eliciting a passive metastatic calcification process, raised Ca and P levels have an active role in changing VSMCs phenotype [15], as detailed later.

Fetuin-A (α -Heremans Schmid glycoprotein, AHSG) is a circulating inhibitor of vascular ossification-calcification synthesized in the liver. Due to its high affinity to hydroxyapatite, it tends to accumulate in calcification sites. Its transient effects are mediated by “calciprotein particles”, which clear circulating Ca and P and therefore selectively inhibit vascular ossification-calcification without interfering in bone mineralization [18]. Fetuin-A is also a TGF- β antagonist, acting at a cellular level and interacting with inflammatory mediators involved in osteogenesis. As a negative acute-phase reactant, fetuin-A was shown to be downregulated in inflammatory states, CKD and CUA patients, which is favourable to vascular ossification-calcification [13, 19, 20].

Besides serum, ECM also makes a contribution towards a pro-calcifying milieu. ECM remodelling is now seen as an early event of CUA: according to recent autopsy studies of skin lesions of CUA, there is a marked upregulation of several ECM proteins indicating extensive matrix remodelling in the subcutis [21]. These proteins, such as osteopontin, collagen I, fibronectin and laminin, create a pro-calcifying ECM environment as they are involved in biomineralization [5]. Another critical ECM protein in CUA is the matrix GLA protein (MGP), which may be seen as the ECM equivalent of fetuin-A.

MGP is a constitutive ECM protein that inhibits vascular ossification-calcification. Like fetuin-A, it is particularly present where vascular ossification-calcification happens, and it is synthesised in VSMCs. Active MGP forms complexes with fetuin-A and inhibits BMP-2-induced osteogenic differentiation [18, 22]. γ -Carboxylation is a vitamin K-dependent enzymatic reaction necessary for MGP activity [23]. Thus, vitamin K deficiency leads to increased uncarboxylated (inactive) MGP in calcification sites, with a corresponding decrease in its circulating fraction. According to ELISA-based studies, inactive MGP is systematically depleted in the serum of CUA patients [24].

VSMCs actually make calcification happen

Arteriolar biomineralization basically consists of crystal nucleation and propagation with hydroxyapatite deposition in the arteriolar media [3, 5] and is actively performed by VSMCs. VSMCs are pluripotent [9] and may undergo transdifferentiation from a contractile to an osteochondrocytic phenotype, necrosis or apoptosis [25]. These different cellular transformations can promote medial calcification in dif-

ferent ways. Recently, numerous molecules and signalling pathways have been studied in the VSMCs of CUA and CKD patients [15, 26, 27]; their extensive analysis goes beyond this review.

VSMCs shift into an osteochondrocytic phenotype makes them capable of active osteogenesis. This transformation is mainly attributed to inorganic phosphate and presumably does not happen in its absence [28]. In addition, uremic toxins, reactive oxygen species, proinflammatory cytokines, hypercalcemia, BMP-2 upregulation in endothelial cells and decreased levels of constitutive calcification inhibiting proteins are thought to play a concurrent role by themselves or through facilitation of phosphate action [9, 13]. Phosphate enters VSMCs via Pit-1 (NaPOC), a sodium-dependent phosphate cotransporter. Through this protein, elevated serum phosphate levels translate into increased cytosolic phosphate, which in turn upregulates the transcription factor Runx2 (Cbfa-1), promoting differentiation of VSMCs into a secretory phenotype. A prominent feature of these cells is the ability to release mineralization-competent matrix vesicles [29].

Thus, the secretory phenotype corresponds to a proper adaptation of VSMCs to a high phosphate environment. VSMCs that maintain their contractile phenotype are said not to be adapted.

Besides phosphate, systemic hypercalcemia and a pro-calcifying local and systemic milieu seem to explain further changes in both adapted and non-adapted VSMCs [30].

As a result of these stimuli, secretory (adapted) VSMCs undergo osteochondrocytic differentiation, with increased osteopontin and decreased α -actin expression [9, 31]. Consequently, production and release of matrix vesicles is increased and nanocrystals are endocytosed and released into the pro-calcific ECM. Release of matrix vesicles is a protective mechanism by preventing intracellular calcium overload, but induces ECM calcification [3]. Finally, uptake of nanocrystals by VSMCs induces their senescence and apoptosis and triggers new cycles of osteogenic differentiation via BMP-2 and osteopontin upregulation [30, 32].

On the contrary, contractile (non-adapted) VSMCs cannot defend themselves from calcium overload, which, in the context of high phosphate, triggers their necrosis. Apoptotic and necrotic VSMCs are thought to be a nidus for calcification, enhancing the whole process [25].

It should be reemphasized that vascular ossification-calcification, albeit necessary, is not enough to cause tissue necrosis [12]. Along with medial calcification, VSMCs may promote arteriolar stenosis and occlusion through mechanisms interconnected with endothelial cells: intimal hyperplasia and sloughing of vascular cells.

Intimal hyperplasia is the universal healing response of the vessel wall to insults. Endothelial cells dysfunction and injury trigger an inflammatory reaction with release of mediators inducing VSMCs migration to the intima, proliferation and synthesis of ECM. The consequence of this process is the formation of a permanently thickened neointima, causing arteriolar stenosis [13].

Sloughing of vascular cells (VSMCs and endothelial cells) into the vessel lumen may be favoured by increased osteopontin expression by VSMCs [31] and results in non-thrombotic arteriolar occlusion.

Endothelial cells add up to the problem

The effect of oscillatory shear stress, inflammatory cytokines and reactive oxygen species (ROS) cause BMP-2 upregulation in endothelial cells inducing VSMCs' osteochondrogenic transdifferentiation [5].

Endothelial cells contribute to arteriolar stenosis and occlusion through dysfunction, injury, necrosis and hyperplasia.

Endothelial dysfunction consists of complex changes in endothelial cells biology and occurs in a broader context of chronic cardiometabolic comorbidities and inflammation. The synthesis of the vasodilator nitric oxide is decreased, which causes vasoconstriction; there is also a preferential synthesis of pro-coagulant molecules [15]. Increased ROS formation potentiates nitric oxide depletion and leads to injury of endothelial cells [9].

Injury of endothelial cells arises from endothelial dysfunction and vascular ossification-calcification. Injured endothelial cells eventually suffer necrosis and slough into the vascular lumen, promoting subintimal fibrosis, non-thrombotic occlusion and thrombogenesis. Histologic studies found destruction of the endothelial layer, detached endoluminal CD31+ endothelial cells and signs of total occlusion in subcutaneous arterioles of CUA patients [5].

Hyperplasia of endothelial cells (not to be confounded with intimal hyperplasia) is an associated histological finding of CUA [13] which might cause further arteriolar stenosis. BMP-4 may be one of the culprits of this proliferative activity of endothelial cells [5].

Surrounding tissues may also calcify: the Selye's CUA

Simultaneously to medial arteriolar calcification, there may be calcified deposits in the extravascular structures, which in general is associated with more severe CUA [8].

One of the possible explanations for the presence of ectopic calcium deposits involves the adipocytes. Altered adipocyte biology is one of the hallmarks of chronic inflammation with increased production of adipocytokines, boosting local and systemic inflammation [13].

Inflammation and associated necrosis of subcutaneous adipose tissue (panniculitis) are thought to disseminate calcium deposition [5], producing deposits in adipose lobules, interadipocyte spaces and subcutaneous septa.

Rare cases of CUA have been described where the most prominent pathologic features are soft tissue calcification and necrosis. These patients belong to an extreme of the spectrum of CUA termed "tissue calciphylaxis" or "calcifying panniculitis". Another interesting fact about these cases is the well-defined cause-effect relationship between specific precipitating factors, such as injection of iron-dextran or calcium heparinate, and CUA [33, 34]. This way of inducing the disease is strikingly similar to the concept of calciphylaxis first introduced by Hans Selye, who performed experiments in animals exposed to a set of sensitization and challenging factors [11, 35, 36].

Despite the differences between experimental and human CUA, Selye's focus on sensitizing and challenging factors may be useful to understand some links between the disease and the complexity of the CUA patient.

Clinical aspects

Risk factors: seeing the patient as a whole

According to the original definition of CUA as a condition of anaphylactic hypersensitivity, this disease would result from the exposure of a previously sensitized ("allergic") patient to external challengers ("allergens") [35, 37]. Even though human CUA is not currently regarded as an allergic disease, this

model remains useful in clinical practice: in the CUA patient, a timely recognition and removal of both sensitizing and challenging etiologic agents is key to treatment [12, 38].

It is unclear whether some factors involved in this disease are actually causative or only associated. This distinction is relevant because associated factors help to identify patients at risk of developing CUA, but only true causative factors guide treatment [21, 39]. For instance, hypoalbuminemia is a marker for malnutrition and mortality in CKD patients with a strong association with CUA, because it is linked to chronic inflammation, dermal loss in ulcerated lesions and reduced fetuin-A levels. However, this factor probably does not participate in the pathogenesis of CUA [9, 20]. Randomized controlled trials would provide the most accurate confirmation of causality; however, the design of such studies would be a challenge, considering the rarity of CUA. Due to this limitation, several case-control studies have been performed to identify statistically significant risk factors for the development of CUA. Some of the variables consistently associated with CUA include white race, obesity, warfarin and calcitriol therapy and elevated serum calcium levels; CUA registries may be helpful in the verification of these associations [40-43]. Also, some therapies are risk factors: iatrogeny is thought to play a prominent role in the development of CUA [20].

Sensitizers confer predisposition to CUA by creating a systemic pro-calcification and pro-inflammatory milieu. These agents define the patient's clinical profile: CUA is found in both uremic and non-uremic patients, who differ in their clinical backgrounds and sensitizers.

Uremic CUA occurs in patients with advanced CKD, mainly stage V on chronic dialysis or after renal transplantation, and represents the majority of the cases [6, 12, 13]. Hyperphosphatemia, hypercalcemia, increased CaXP and secondary hyperparathyroidism are thought to play a central role in the development of CUA [38, 44]. High calcium and phosphate diet, treatment with calcium-containing phosphate binders and active vitamin D analogs may exacerbate this type of systemic sensitization [13, 44, 45]. Therefore, a tight metabolic control is an important effort for successful treatment [13].

Non-uremic CUA has been increasingly recognized and affects patients with preserved renal function [4, 9, 13]. It is more commonly described in primary hyperparathyroidism. This non-uremic CUA has also been reported in patients with autoimmune diseases, chronic inflammatory states, such as Crohn disease, connective tissue diseases, sarcoidosis, alcoholic liver disease, and malignant neoplasms [6, 46, 47]. In patients with autoimmune diseases, CUA is often incorrectly diagnosed as a vasculitic process [47]. It should be noted that autoimmune conditions may also contribute to the development of CUA in

uremic patients [48]. Thus, anti-inflammatory and antioxidant approaches should be part of the treatment of both uremic and non-uremic CUA [13].

Uremic and non-uremic CUA patients may share other sensitizers not directly related with inflammatory diseases. Obesity, type II diabetes mellitus, female gender and hypercoagulability may elicit CUA by distinct mechanisms. Obesity may compromise arteriolar blood flow to skin and subcutaneous tissues and potentiates arteriolar thrombosis. Type II diabetes mellitus is associated with kidney disease, inflammation and platelet aggregation, which contribute to renal function impairment, endothelial dysfunction and arteriolar thrombosis, respectively [9, 38]. Females have a predominantly proximal adipose tissue distribution, where CUA is more common, and hormonal influences (estrogen and leptin) may play a role [39]. Hypercoagulability is a systemic influence towards arteriolar thrombosis arising from protein C or S deficiency, obesity or antiphospholipid syndrome [6]. Low molecular weight heparin and tissue plasminogen activator have been shown to successfully heal skin lesions in CUA patients supporting the role of hypercoagulability [49].

In a sensitized uremic or non-uremic patient, challengers act as external acute triggers which precipitate or aggravate clinical manifestations of CUA [20]. Subcutaneous injections, corticosteroids, warfarin, antineoplastic drugs, iron salts, erythropoietin and albumin are some potential iatrogenic causes [6, 9, 35, 46, 50]. All these etiologies are plausible in practice because, in most cases, CUA patients are thoroughly followed by nephrologists or internists and, therefore, potentially exposed to overtreatment [20, 39].

Warfarin, a vitamin K antagonist commonly used in dialysis patients, inhibits γ -carboxylation reactions, required for the activity of MGP, an anti-calcifying protein located in the ECM. Consequently, warfarin increases vascular ossification-calcification processes, which may explain the strong association between warfarin use and the development of CUA [20, 40, 41, 44].

This division of risk factors into sensitizers and challengers underscores the importance of preventive strategies in the management of CUA, but fails to explain why very few uremic patients actually develop the disease even if exposed to challenging factors [12, 39].

It is clinically relevant to identify the very distinct uremic and non-uremic individuals who may potentially develop CUA. Moreover, diagnosis is even more difficult in non-uremic patients, requiring a high index of clinical suspicion [51]. However, non-uremic patients ultimately develop the identical clinical presentation and histopathologic findings of classic CUA [13].

Painting the clinical picture and ruling out differential diagnoses

Due to the clinical heterogeneity of CUA in both uremic and non-uremic patients, subgroups of the disease with distinct prognoses have been proposed [20, 39]. Skin involvement is more frequent; rare cases of CUA affecting internal organs have also been described [52].

Visceral CUA has been identified in post-mortem examinations of critically ill patients. Reported clinical presentations include acute respiratory failure [52, 53], gastrointestinal bleeding [54] and widespread visceral involvement in a patient with primary autoimmune myelofibrosis [51]. A recent investigation has questioned the actual existence of non-cutaneous CUA, pointing the lack of definitive histopathologic evidence in some of these autopsy cases [55]. Furthermore, some systemic manifestations associated with cutaneous CUA may result from extracutaneous calcification processes not necessarily related to visceral CUA [36]. Taking these ideas into consideration, visceral CUA will not be further discussed in this review.

Cutaneous CUA typically presents as a biphasic process [44, 56]. Each phase may be understood as a set of clinical consequences of specific histologic lesions belonging to a continuum towards tissue necrosis. ECM remodelling, medial calcification and arteriolar stenosis could be considered “primary lesions”, whereas thrombus formation and luminal obstruction leading to tissue infarction have been postulated as “secondary lesions” [13, 39]. Primary and secondary lesions might be associated with the first and second clinical phases, respectively.

Phase one usually starts with areas of skin leather-like induration with superimposed pruritic and excruciatingly painful erythematous nodules, plaques or livedo reticularis. These lesions are more prone to appear at adipose tissue sites and become progressively deeper and more extensive.

Phase two consists of painful ischemic necrosis which manifests as non-healing ulcerations and black deep eschars. Infection, abscess formation and gangrene frequently follow the appearance of these lesions [6, 9, 10, 35, 36, 38, 56].

Acral, distal and penile lesions have a more favourable clinical course, whereas lesions with proximal distribution carry a worse prognosis [20, 35, 36, 39, 50].

Clinical conditions with prominent vascular involvement and dermatologic manifestations similar to CUA belong to an extensive list of differential diagnoses. Some of these diseases are highly prevalent or carry a fatal prognosis and must be promptly excluded, namely peripheral artery disease, autoimmune

vasculitis, diabetes mellitus-related lower extremity involvement and cholesterol embolization [6, 9, 35, 39, 44, 57, 58]. In some situations, these diseases may coexist with CUA and should be treated accordingly.

In a patient presenting with skin lesions suggesting CUA, a thorough clinical history should be obtained, with particular emphasis on risk factors, and complementary exams need to be performed in order to rule out differential diagnoses and establish a definitive diagnosis of CUA [6]. Biochemistry, histopathology and imagiology are the three main vectors of diagnostic investigation, but negative results should not be regarded as a warranty of exclusion of the disease [36].

Laboratory findings are unspecific, variable and dependent on underlying pathologies. Hyperphosphatemia, increased CaXP, hyperparathyroidism and slight hypercalcemia may be found in uremic patients; elevated canalicular enzymes and albumin are other possible findings in all CUA patients. However, both uremic and non-uremic CUA patients may present without these biochemical changes: usage of medications in an attempt to correct these metabolic parameters may be one of the reasons for this clinical fact [15, 17, 36, 59].

Deep skin and subcutaneous tissue incisional biopsy with calcification-sensitive (von Kossa) staining is the gold standard for definitive diagnosis [6, 9, 10, 13, 58]. There is controversy on whether biopsy should be routinely performed, because this procedure may induce novel non-healing ulcers, existing lesions may become more difficult to heal and easier to superinfect and there may be false negative results [6, 8, 20, 44, 58, 60]. Our institution adopts a very restrictive approach to the use of skin biopsy, whose execution is decided on a case-by-case basis, according to the clinical experience of each nephrologist. Histopathologic findings in CUA, albeit specific, are not pathognomonic and may include one or more of the following: medial arteriolar calcification without associated intimal calcification or vasculitic changes, intimal hyperplasia, ECM remodelling, soft tissue calcification, thrombosis, epidermal ulceration and dermal or subcutaneous necrosis [6, 13, 20, 36].

Imaging modalities may be useful to support histologic results, avoid biopsy or monitor response to treatment [61]. Plain soft tissue radiographs may show a typical net-like pattern of vascular calcification and irregularity of the soft tissues [8, 61]. Mammography technique is thought to be superior to plain-soft tissue x-ray, because it is safe, inexpensive and able to delineate high-contrast microcalcifications which cannot be identified in other radiography exams; the main disadvantage of this exam is that it requires the compression of the lesions between two plates, causing intense pain [6, 58]. Xeroradiography is described

by some authors as the optimal way of studying arteriolar and soft tissue calcifications [17, 36, 44]. Bone scintigraphy with Tc99m methylene diphosphate detects increased soft tissue uptake of bone tracer in areas with noticeable clinical expression, but lacks sensitivity and specificity [8, 39, 44, 57, 60].

Once the clinical picture is fully identified and a definitive diagnosis is obtained, patients should promptly receive specialized care. However, therapy should ideally begin early in the stage of the disease and, many times, before definitive diagnosis.

Therapy: to be started in the early stages of CUA

Treatment of CUA remains a series of experimental interventions lacking clinical evidence, with unrewarding results and controversial impacts on morbidity and mortality [11, 20, 39]. The various pathogenic mechanisms involved in CUA support a multimodal approach targeted at distinct aspects of the disease, although uremic and non-uremic patients are treated similarly.

Active treatment of established CUA tends not to be enough. Despite the impressive clinical picture of advanced CUA, most of the therapeutic measures are not focused on healing visible lesions but rather on treating underlying disease processes and removing iatrogeny [11, 39], which can be done before overt CUA develops. In CUA, therapy may be seen as a continuum starting from prevention, which is a very important proactive strategy for ‘at risk’ patients [62].

Withdrawal of iatrogeny and management of underlying disease processes are the mainstay of prevention and treatment of CUA

Certain medications that may aggravate systemic sensitization or act as challenging factors in the development of CUA should be discontinued, namely vitamin D analogs, subcutaneous injections and warfarin [44, 57]; the latter may be replaced with “safe” anticoagulants, namely low-molecular weight heparin, and administration of vitamin K [9, 20, 39]. Corticosteroids belong to a “grey zone” between iatrogeny and therapy. On the one hand, prednisolone may be an etiologic agent of CUA and increases infection risk of ulcerated lesions; on the other hand, this drug decreases tissue inflammation and has already been shown to be effective in some cases [44, 46, 57].

As far as underlying disease processes are concerned, nutritional status and comorbid conditions of uremic and non-uremic CUA patients require careful monitoring and treatment [6, 44, 46, 63]. In particular, control of metabolic parameters is an essential strategy and may be achieved with interventions targeted at phosphate, calcium, CaXP and/or parathormone (PTH) levels, in order to prevent and treat hyperphosphatemia, hypercalcemia and/or hyperparathyroidism, respectively.

Hyperphosphatemia and hypercalcemia require consideration of more intensive dialysis with low calcium dialysate, replacement of oral calcium phosphate binders with non-calcium phosphate binders and withdrawal of calcium supplementation [9, 10, 13, 39, 50, 57]. Control of hyperphosphatemia should be prioritized over control of hypercalcemia, because phosphate is a requirement for VSMCs to perform their active role of arteriolar calcification. In theory, however, induction of transient hypocalcemia could also prove beneficial to normalize CaXP and remove calcium from tissues [44].

Hyperparathyroidism may be treated medically or surgically. Cinacalcet is a calcimimetic, suppressing PTH secretion and rapidly correcting calcium and phosphate levels [6, 9, 10, 13, 46]. The EVOLVE clinical trial (EValuation Of Cinacalcet Hydrochloride (HCl) Therapy to Lower CardioVascular Events), an event-driven cardiovascular outcomes study, involved the randomization of 3883 hemodialysis patients with secondary hyperparathyroidism to receive cinacalcet or placebo. 24 patients developed CUA, 18 in the placebo group and 6 in the cinacalcet group. According to a post-hoc analysis of the results of the EVOLVE trial, reduction of serum PTH levels with cinacalcet therapy reduced CUA incidence by 70%, with a hazard ratio (cinacalcet versus placebo) of 0.25 [64]. For patients with unsatisfactory response to medical treatment and evidence of high bone turnover, parathyroidectomy has been proposed [9, 10, 13, 20, 46, 57, 65, 66]. Despite the risks of the procedure and unproven benefits on survival, this surgery may improve wound healing and tissue oxygenation, especially in patients with very high PTH levels [6, 9, 11, 12, 44].

As outlined above, CUA may happen in the context of a normal Ca-P metabolism. Thus, systemic therapies with antioxidant, anti-inflammatory and antithrombotic mechanisms of action are also used in both uremic and non-uremic patients [13].

Sodium thiosulfate: a step forward in therapy

Sodium thiosulphate (STS) is currently regarded as the first-line treatment of patients without hyperparathyroidism [6, 13, 46, 50, 57].

The mechanism of action of STS is unknown; dissolution of calcium deposits, chelation of calcium ions, antioxidant effects and potent vasodilation are some possible effects [6, 9, 11, 13, 39, 46, 57, 67].

In 2004, Cicone et al. reported the first successful treatment of CUA with STS, which took inspiration from previously reported cases of tumoral calcinosis responsive to STS. Dramatic improvements in algic complaints, subcutaneous lesions and technetium 99 scans were observed. Also, STS did not produce any effects on Ca-P metabolism, which suggests the use of this drug in tandem with a rigorous metabolic control. According to these authors, STS could be particularly beneficial in patients unresponsive to other therapeutic measures [68].

Potential adverse effects of long-term usage of STS remain a concern, especially bone demineralization due to STS-induced metabolic acidosis [20]. Other side effects, namely nausea, vomiting, headache, hypotension and electrocardiographic abnormalities, have also been described [9, 13, 20, 46, 57].

Other strategies also belong to the unfinished equation of therapy

Bisphosphonates are widely used to treat osteoclast-mediated bone loss and have been shown to be capable of treating tumoral calcinosis and preventing experimental CUA. These assumptions motivated the first use of pamidronate by Monney et al. in the treatment of a patient with rapidly aggravating CUA and CKD. Forty-eight hours after the initiation of treatment with pamidronate, a marked improvement in the clinical course, with pain reduction and ulcer healing, has been observed [69]. Subsequent studies also demonstrated favourable clinical outcomes, which may be mediated by a decrease in inflammation, inhibition of arteriolar calcification and reduction of serum calcium levels through suppression of osteoclastic activity. Bisphosphonates have been shown to be effective and well-tolerated, but their use should be cautiously considered due to potentially deleterious effects on bone metabolism and renal function [6, 9, 12, 13, 20, 39, 46, 57, 63].

Hyperbaric oxygen (HBO) therapy consists of breathing 100% oxygen in a pressurized environment, increasing the amount of dissolved oxygen in the plasma, counteracting local tissue hypoxia and improv-

ing wound healing. Also, HBO is directly bactericidal and bacteriostatic and stimulates neutrophil bactericidal activity, angiogenesis and fibroblast proliferation. Middle ear barotrauma, pulmonary and central nervous system oxygen toxicity, claustrophobia and high monetary costs are some potential problems of HBO therapy. Despite its limitations, HBO therapy has been shown to be beneficial in several case reports and retrospective case reviews, especially in patients with distal CUA without secondary hyperparathyroidism, without surgical conditions or refractory to parathyroidectomy [6, 9, 13, 39, 44, 46, 70].

According to a matched case-control study, statins may prevent CUA development in dialysis patients. Anti-inflammatory, antithrombotic and anticalcification properties of these drugs may underlie this association between statin use and CUA. Should this association be corroborated, statins may become an important strategy for CUA prevention [41].

Besides systemic therapies, advanced CUA lesions also require intensive local wound care and pain management. Some therapeutic options include debridement of gangrenous tissue, use of broad-spectrum antibiotics for superimposed bacterial infection, sterile dressings and pain schedule with opiates [6, 9-11, 13, 17, 39, 44, 46, 56, 57, 60].

Conclusion

Prognosis of CUA remains poor. Local and systemic infectious complications are responsible for short survival and 5-year mortality rates around 60-70% in CUA patients, even when aggressively treated with large-spectrum antibiotherapy [9, 10, 17, 36, 57, 66].

In this increasingly recognized disease, there is still much to be elucidated on the pathogenesis. According to our revision of the literature, vascular ossification-calcification phenomena in CUA are basically similar with common uremic vascular ossification-calcification events; however, these mechanisms might not explain vascular ossification-calcification in non-uremic patients, where inflammation probably assumes a prominent role. As far as diagnosis is concerned, an early identification of 'at risk' uremic and non-uremic patients is a crucial step for a more successful treatment. Targeted therapies have been mentioned in the literature as a promising innovation in the management of CUA [6, 10]. However, it is likely that prevention, multidisciplinary care and avoidance of iatrogeny should remain the foundations in the management of CUA [11, 20, 45, 50, 56, 66].

In summary, many questions on fundamental aspects of this complex disease are yet to be answered, deserving further attention by investigators and clinicians.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Fig. 1 Calcific uremic arteriolopathy: a multi-layered pathogenesis. This diagram outlines the main events in the arteriole and adjacent tissues. From the top to the bottom, like a transverse section of an arteriole: lumen; tunica intima; tunica media; extracellular matrix of the arteriole; adipocytes and extracellular matrix of the surrounding dermis, hypodermis or other soft tissue or visceral structure. Various influences between systemic and local factors and events were not depicted for clarity. The black box signals the main event and histologic finding of calcific uremic arteriolopathy. Gray boxes mark associated structural changes which can be found in calcific uremic arteriolopathy. See text for further details. *Ca* calcium, P_i inorganic phosphate, *CaXP* calcium-phosphate product, *VSMCs* vascular smooth muscle cells, *MGP* matrix GLA protein, *BMP* bone morphogenetic protein

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