Review Article :

Calcific uremic arteriopathy (calciphylaxis) multidisciplinary approach narrative review

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Abstract

Background & Aims:

Background: calcific uremic arteriopathy or calciphylaxis is a rare condition. The condition is fatal, with high mortality. A multidisciplinary approach is essential and useful in such patients.

Review the therapeutic options for calcific uremic arteriopathy. And to provide a smooth and applicable reference for a multidisciplinary team treating patients with calcific uremic arteriopathy.

Methods:

We searched PubMed, Medline, the Cochrane Library, and Embase for calcific uremic arteriopathy and calciphylaxis.

Conclusion:

calcific uremic arteriopathy is a life-threatening condition. There is no consensus on a unified management protocol. In such a situation, we have to apply our basic sciences knowledge and treat patients accordingly to provide a clear plan and enroll such patients in studies to end up with clear guidelines.

Keywords:

Calciphylaxis, Calcific uremic arteriopathy, Secondary hyperparathyroidism.

الملخص

الخلفية و الاهداف :

اعتلال الشرايين الكلسي البولي أو التكلسي هو حالة نادرة. الحالة قاتلة مع ارتفاع معدل الوفيات. نهج متعدد التخصصات ضروري ومفيد في مثل هؤلاء المرضى.

مراجعة الخيارات العلاجية لاعتلال الشرايين المتكلس البولي. لتوفير مرجع سلس وقابل للتطبيق لفريق متعدد التخصصات يعالج المرضى الذين يعانون من اعتلال الشرايين البولي الكلس

طريقة البحث :

بحثنا في PubMed و Medline ومكتبة Cochrane و Embase عن اعتلال الشرايين المتكلس اليوريمي والتكلس التكلسي.

الخلاصة:

اعتلال الشرايين الكلسي البولي أو التكلسي (CUA)هي حالة تهدد الحياة. لا يوجد إجماع على طريقة علاج موحدة في مثل هذه الحالة ، يتعين علينا تطبيق معرفتنا بالعلوم الأساسية وعلاج المرضى وفقًا لذلك لتوفير خطة واضحة وإدراج هؤلاء المرضى في الدراسات حتى ينتهي الأمر بإرشادات واضحة.

Introduction:

The term calciphylaxis is a word of two portions, "calci" means calcification, and "phylaxis" means protection. The term was introduced by Dr. Seyle in 1961[1] when he described a skin shell in rats that took high parathyroid hormone (PTH) or vitamin D. Calcium deposits on the rat's skin and form shells at the site of minor skin trauma; subsequently, these shells creep out, and new skin forms. The scientists thought that calciphylaxis in the renal patient is similar to that developed in the rat's skin. However, the mechanism included the same milieu (high phosphate and parathyroid hormone) and the same dermis deposition. In renal patients, healthy skin doesn't replace the skin shells. In rats [1], the calcium deposition occurs in the skin only; however, in humans, it involves both skin and blood vessels. Further, in humans, the skin lesions are associated with ischemic signs; thus, this is not a protective mechanism, and based on that, the term calcific uremic arteriolopathy was introduced.

The yearly incidence of calcific uremic arteriopathy (CUA) among renal patients varies from 0.4 – 4 2 and the ischemic skin lesions are at high risk of infection; hence the condition is life-threatening. Risk factors include [2,3] female gender with end-stage renal disease (ESRD), abnormal vitamin D, phosphate, calcium, hypo- or hyperparathyroidism, and hypoalbuminemia. Vascular endothelium and smooth muscle secret molecular calcifications inhibitor matrix Gla protein (MGP). Vitamin K is essential for MGP activation. So, vitamin K deficiency in the renal patient either by warfarin or by low vitamin intake leads to MGP dysfunction which result in more calcification and development of calcific uremic arteriopathy (CUA). Protein C is a vitamin K dependent factor, and it is natural anticoagulation, vitamin k deficiency, makes it less effective. It may play a role in CUA pathogenesis. As a recommendation from national kidney foundation in united states 4 the following values should be maintained to decrease the risk of CUA in hemodialysis patients; serum calcium concentration of 8.4–9.5 mg/dL, serum phosphate concentration of 3.5–5 mg/dL and an intact parathyroid hormone concentration of 150–300 pg/mL.

CUA is diagnosed clinically in ESRD patients. Typically, the patient presents with [2, 5] indurated, abdominal tenderness, or legs skin chronic ulcers or plaques. The punch biopsy of 3-5 mm is indicated in non-uremic patient with atypical presentation [5]. Pyoderma gangrenosum, cholesterol emboli, Purpura fulminans, and Warfarin-induced necrosis are differential diagnosis [2]. The skin biopsy is contrain-

dicated in an infected skin lesion, [6] and it might lead to the formation of new lesions. Histopathology features include epidermal ulceration, focal dermal necrosis, and vascular calcification [7,8]. The best treatment is prevention by modification of modifiable risk factors, such as correction of vitamin D, phosphate and, calcium levels. However, once a high-risk patient presents with pain, full nonhealing abdominal or leg skin ulcer, or plaque, a multidisciplinary approach should be initiated by (nephrologist, dermatologist, wound care team, nutritionist and endocrine surgeon). The target of the group is to confirm the diagnosis and to start management. There is no evidence-based treatment; however, the management approach should focus on the following aspects:

- *Pain.*
- *Wound care.*
- *Correction of minerals disturbance.*
- *Elimination of eliminable risk factors.*
- *Prevent further calcium deposition in the skin and blood vessels.*
- *Correction of uremia.*
- *Correct of hypercoagulability.*

Pain management:

CUA pain is ischemic and needs special care. Knowing the pharmacological properties of the analgesia in the renal patient is the cornerstone as they need many analgesias. The use of the synergetic effects of several analgesics can give good results. Dose manipulation of analgesia for the renal patient is dependent on the renal impairment severity and if the patient is on dialysis. Opioids are the best analgesic for renal patients with CUA. Avoid morphine[9] as it has active metabolites that cause respiratory depression. Consider abuse and misuse. Some studies showed sodium thiosulfate relief the pain in CUA renal patients [2] before wound healing. The intramuscular and subcutaneous injection must be avoided [10] to prevent the formation of plaques and ulcers at the site of injection. Nephrologists and clinical pharmacists should take this part of management.

Wound care:

General principles of modern wound care, in addition to the general morbidity of the patient and hypoxic wound due to ischemia, must be kept in considerations. Wound care specialist is essential, and a professional wound care center is preferable for wound's care of CUA ulcers. Type of dressing, the role of debridement, prevention of infections, and wound oxygenation are general concepts of wound care in such patients.

The type of dressing is preferred to be non-adhesive or products with silicon layers [11] to decrease trauma and pain during redressing.

Topical antibacterial agents are an attrac-

tive option to be applied during dressing in infected wounds.

The surgical debridement is controversial and must be individualized. Debridement of dead tissue decreases bacterial overgrowth and improves wound healing. Still, it is excruciating, and it increases the risk of a new lesion formation at the site of trauma; it resembles skin biopsy. So, if the debridement is mandatory [11], it should be done gently with analgesia to be given to the patient before the procedure to decrease the pain. Chemical debridement, as well as maggot therapy, is advised by some authors [12] especially for non-infected, dry wounds.

The wound oxygenation was tried invasively by revascularization of the affected leg [10] and had poor result. The unfortunate results are due to the poor general condition of the patient and the nature of the disease as it affects the small and medium blood vessels and not large ones.

As a non-invasive method of oxygenation, hyperbaric oxygen (HBO) therapy, theoretically it improves the fibroblast function, angiogenesis, and promotes healing. Jennifer AN et al. retrospective case series study of 34 cases [13] showed an improvement of 58% with complete healing in 50%; on the other hand, deterioration was observed in 38 %. The adverse effects of HBO therapy are claustrophobia and middle ear barotrauma. The systemic review [24] did not demonstrate a promising efficacy of HOB on CUA lesions.

Wound care specialists and surgeons are the responsible persons in wound management.

Correction of minerals disturbance:

Controlling of hyperphosphatemia is crucial [11] in the treatment of CUA cases. Frequent hemodialysis, non-calcium phosphate chelating agents, and phosphate intake restriction are actions to decrease the phosphate level. The target phosphate level in CUA patients [14] is 3mg/dl. Isolated hyperphosphatemia can cause CUA.

The serum calcium level should be optimized, and the target level [2] is 8mg/dl. Restricted calcium and vitamin D diet[8], increase the frequency of dialysis with avoidance of high calcium dialysate, cinacalcet, parathyroidectomy; all are used to correct the patient's calcium level. If medical therapy fails, then parathyroidectomy is indicated.

Surgery is a risky option in such patients; the optimal time of surgery is not yet determined. Some studies [15,16] showed improvement after surgeries other show deterioration. Duffy et al. study [17] showed complete wound healing and survival rate improvement of [6] patients after parathyroidectomy out of [15] patients. The limitation of this retrospective study is a limited number, and

all six parathyroidectomies younger patients and their general clinical conditions are better than the conservative group. Another single-institution retrospective study. Forty-nine patients by Weening et al. [18] sixteen of them underwent parathyroidectomy, and the study showed a 33% one-year survival rate of parathyroidectomy patients versus 38% of medically treated patients, wound improvement, and patient's conditions were not provided. Lal et al. retrospective study [19] showed wounds and survival rate improvement of patients who underwent surgical intervention of lesion and parathyroid. The first and third studies mentioned above showed surgery is more beneficial for patients with high parathyroid hormone. Kang et al. [20] advocated that the benefit is likely to be more in patients with very high PTH. The authors who take the PTH level as an indicator for parathyroidectomy [16] the PTH level ranges between 500-800pg/ml. The PTH shouldn't be lower than 100pg/ml [21] at this level; there is a risk of calcium deposit outside the bone and threat of more CUA lesions. Total parathyroidectomy was the only cause of CUA in some reports [22]. Patrick et al. [23] suggested a new approach dependent on the bone metabolism status. The hyperdynamic bone disease patients benefit from lowering their parathyroid hormone (medically or surgically) more than patients with adynamic bone disease patients who might need recombinant parathyroid hormone (hrPTH) to treat their CUA lesions bone biopsy is necessary to evaluate the bone metabolic status. This approach supports the older studies, which showed that the patients with high PTH and underwent parathyroidectomy has better survival and wound healing rate. However, parathyroidectomy can improve the CUA lesions in patients with high PTH and hyperdynamic bone disease theoretically, but it lacks evidence-based support. The recent systemic review [24] showed that patients who underwent parathyroidectomy have a better survival rate. The benefit of parathyroidectomy in this systemic review attributed the patient's selection as most of those patients were fit and younger than no parathyroidectomy group. Surgery or no surgery must be tailored according to patients' condition, and the decision depends on the failure of medical therapy, bone metabolism status, and operability of the patient. We doubt the benefit of urgent parathyroidectomy as there are medications that can control the hormone level till the patients' general condition improve, then surgery can be done as an elective procedure to treat hyperparathyroidism rather than treating CUA. Up to this date, there is no strong evidence-based recommendation for urgent parathyroidectomy versus

no parathyroidectomy.

Elimination of eliminable risk factors:

Risk factors must be well determined for any disease. The determination of risk factors can help in two ways; first, modifying the modifiable risk factors impact positively on the affected patients second can help to plan the prevention of development of disease in unaffected patients. A Nationally Representative Study of Calcific Uremic Arteriolopathy Risk Factors [25] showed that the median time for CUA to develop after initiation of dialysis is 925 days, and it gives proper time to modify the modifiable risk factors. The same study confirms the risk factors that showed by older studies. Diabetes, low albumin level, body mass index >37kg/m2, female gender, and the white race are all confirmed risk factors when they present at the initiation of hemodialysis.

High albumin, corrected serum calcium level, and high PTH all are essential risks for CUA. The use of warfarin and vitamin K deficiency are risk factors. The insulin injection site can precipitate for central CUA due to trauma [26,27]. Phosphate binders both (calcium-containing and non-calcium-containing binders) did not show [25] an increase in the odd ration of CUA development. The use of vitamin D supplementation increases the odds ratio of CUA; on the other hand, the use of an active form of vitamin D does not show the same association. The use of erythropoietin and high hemoglobin level decreases the odds ratio of CUA development. The evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial showed [28] that there is a CUA risk reduction in the cinacalcet arm. The recommended PTH level must be between 2-9 times of normal to prevent adynamic bone disease.

Prevent further calcium deposition in the skin and blood vessels:

Correction of uremia by intensive hemodialysis with low dialysate calcium [29]. improves the calcium and phosphate levels and decreases the chance of calcium deposition. Sodium thiosulphate (STS) distributes in the extracellular compartment when it is administered intravenously. STS combined with tissue calcium to form thiosulphate calcium salt. The thiosulphate salts are the most soluble salts among other calcium salts in the body; hence it decreases further deposition of calcium salts and improves the lesions in around 70% of CUA patients as this shown by Peng et al. meta-analysis 30 and other case series [31]. STS is a vasodilator, and anti-oxidant [32] prevents further calcification and ischemia and improve pain and healing when injected directly in the lesion [2,33]. Very low PTH leads [21,34] to more deposition of calcium in

soft tissues so, severe hypoparathyroidism should be avoided in CUA.

Correction of uremia:

Correction of uremia by intensive dialysis has a positive effect on the general condition of the patient and promotes healing by decreasing further vascular calcification. Nephrologists advise the shifting of peritoneal dialysis patients to low dialysate calcium hemodialysis [29] to correct the calcium and phosphate product. PTH is oxidized in the uremic milieu and becomes inactive [23,35] results in adynamic bone disease in hyperparathyroidism patients leads to an increase in the calcium deposition in vessels. So, uremic correction can improve the regular activity of PTH and improve the calcium-phosphate product.

Correct of coagulation:

Most of CUA patients 36 are on warfarin. Such treatment affects the vitamin k dependent coagulation factors 37, including anti-coagulant such as protein C. Several case-control studies showed no relation between protein C and CUA. MGP is a vascular calcification inhibitor that is activated by vitamin K, so; antivitamin K treatment should be quitted in all CUA patients. The patient can be shifted to heparin if anticoagulation is needed. Interestingly several cases of CUA were treated with heparin [38] but there is no reliable evidence to use it as a routine treatment for CUA.

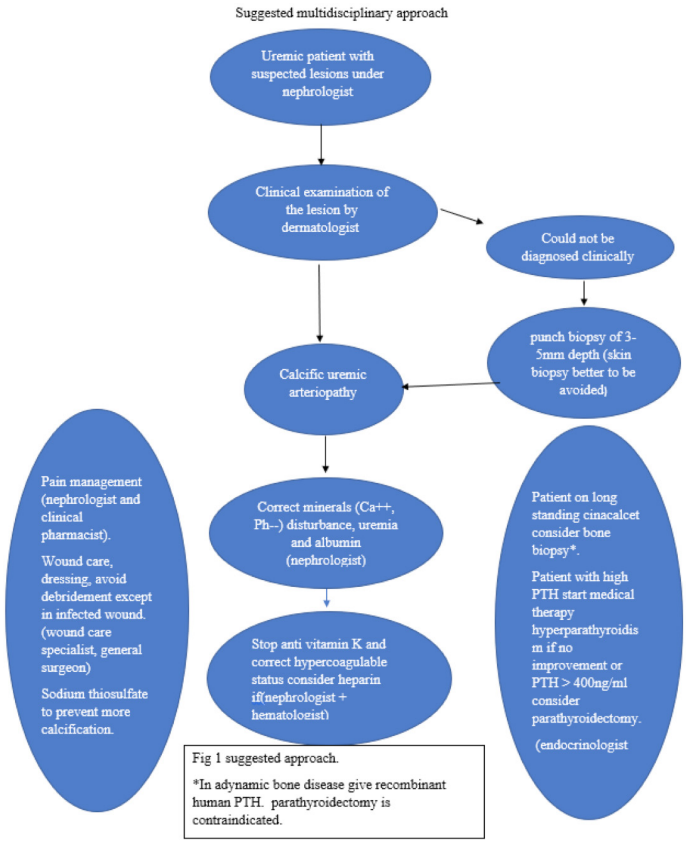

Fig 1 suggested approach.

*In adynamic bone disease give recombinant human PTH. parathyroidectomy is contraindicated.

Conclusion:

CUA is a life-threatening condition. There is no consensus on a unified management protocol. In such a situation, we have to apply our basic sciences knowledge and treat patients accordingly to provide a clear plan and enroll such patients in studies to end up with clear guidelines. Please see figure 1 and for the suggested approach.

Key points:
1. CUA is a rare disease. 2. There is no clear protocol to be followed. 3. Treatment must be individualized. 4. We emphasize a multidisciplinary approach. 5. We emphasize basic knowledge.

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