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Feature Article:

An In-Depth Review of the Use of IV Vitamin D Analogs and Parathyroidectomy in the Management of Secondary Hyperparathyroidism to Treat Calcific Uremic Arteriolopathy in Dialysis Patients.

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Nothing compares with calciphylaxis, or the more clinically appropriate term - Calcific Uremic Arteriolopathy (CUA), as a condition and complication both intriguing and poorly understood in chronic kidney disease. Although it is a relatively rare condition, the related morbidity and mortality rate remains high due to the lack of knowledge related to the pathogenesis of this condtion.

Calciphylaxis or Calcific Uremic Arteriolopathy

Calciphylaxis is an uncommon condition that affects around 1-4% of End Stage Renal Disease patients. It is a vasculopathy occuring primarily in patients with chronic kidney disease. It causes a spectrum of end-organ damage due to ischemia. Sometimes this ischemia can be so severe that it causes infarction to the downstream tissues. The most common and most noticeable cases occur in skin and subcutaneous tissues. The risk of infection increases when the ischemia leads to subcutaneous nodules of infarction and necrotizing skin ulcers that heal poorly. The risk is especially high in regions that posses thicker subcutaneous adipose tissue, such as the breast, abdomen, and thighs. It is a painful condition that develops rapidly and usually leads to ischemic skin necrosis, non-healing ulcers and gangrene that may lead to amputation. Sepsis is the major cause of death; it occurs in approximately 60% of patients who suffer from this condition. Calciphylaxis is usually more prominent in females. The approximate female-to-male ratio is 3:1. It is observed to occur more frequently in Caucasians. It has been reported in individuals ranging from 6 months old to 83 years old. A mean patient age of 48 years was calculated from a large series of patients. It has been observed that younger patients who have received a longer duration of renal replacement therapy, such as dialysis, have a higher chance of developing this condition (1-3).

Vascular calcification was first reported in association with uremia by Bryant and White in 1898 (3). However, uremia, vascular calcification, and skin necrosis were rarely seen. It was not until 1962 that CUA was first properly defined and coined by Selye and colleagues as a “condition of hypersensitivity in which-especially after a sensitization by a specific calcifying factor (e.g. vitamin D compounds, parathyroid hormones)-topical treatment with certain challengers (e.g. egg white, egg yolk, metallic salts) causes an acute local calcinosis followed by inflammation and sclerosis” (4). Selye

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constructed an experimental model and was able to precipitate systemic calcification, somewhat analogous to this syndrome, in nephrectomized rats. It was speculated that a mechanism occurred in uremic humans. They developed a two-step process to generate this condition in rats. The first stage was called sensitization. They sensitized rats with dehydrotachysterol, ergocalciferol, or parathyroid hormone. This was then followed by a challenging stage. Substances used to challenge these rats included intravenous iron, intraperitoneal injections of iron, or intraperitoneal administration of egg albumin. These agents generally induced an inflammatory reaction that later on resulted in calcification. This two-step process was thought to replicate the steps of this visceral organ calcification (5, 6). Since the tissue calcification described by Selye and the clinical syndrome known as calciphylaxis is not an IgE-mediated process, the term "calciphylaxis" hence is considered inaccurate. Given the arteriole involvement in this condition, it is suggested that "calcific uremic arteriolopathy" (CUA) is a more appropriate term for this condition.

Secondary Hyperparathyrodism and Vitamin D Analog Therapy

Secondary hyperparathyrodism (SHPT), usually develops in chronic kidney disease patients as one of the many consequences of renal insufficiency. Although the pathogenesis of CUA is still elusive, SHPT is thought to be closely associated with it. This article will focus on reviewing this particular risk factor. In studies by Selye, rodents were treated with parathyroid hormone used as a "sensitizing" agent. In many reported cases of CUA, serum parathyroid hormone (PTH) values are elevated above acceptable thresholds for end stage renal disease (ESRD) patients (1, 2, 4). One study conducted by Wilmer and colleagues assessed 21 patients with CUA and found their mean serum intact PTH level was 440 +/- 535 pg/dl (7). It remains unknown whether PTH is directly accountable for CUA by causing vascular injury but the role of PTH in the shift of calcium and phosphorus homeostasis has been speculated as a potential cause.

Vitamin D Analog therapy is commonly used in hemodialysis to treat SHPT. In Seyle's model, vitamin D is one of the sensitizers found to stimulate the CUA process. Jono and colleagues suggested that 1,25-dihydroxyvitamin D3 may negatively affect the vascular smooth cell phenotype and cause medial wall calcification (9). In the past vitamin D analog therapy was often one of the first therapies to be eliminated in the treatment of CUA. In contrast to Seyle's model and Jono's theory, recent studies have demonstrated that vitamin D analogs modulate vascular proliferation and upregulate the protective factors of osteopontin and matrix gla protein, and downregulates inflammatory factors, which in turn inhibits vascular calcification (10). Some studies show that lowering serum parathyroid hormone levels and correcting SHPT may help heal ulcerations and alleviate the pain associated with CUA (4, 9, 10). The development of less calcemic forms of vitamin D analogs have reduced the associated risk of induced elevated serum calcium. More recent studies have proposed the use of paricalcitriol or the calcimimetic - cinacalcet in the treatment of CUA as another viable therapy option instead of the traditional surgical parathyroidectomy (11).

Formulating the Clinical Question

In outpatient dialysis clinics settings, dietitians are often assigned the role as the bone mineral managers. A protocol is used as a guideline to adjust patients' phosphate binder and intravenous vitamin D analog therapy. Since CUA is a rare condition, its treatment plan usually is not included within the protocol guidelines. There are no uniform treatment approaches to this condition. Unfortunately regardless of the intervention strategy, outcomes remain poor and mortality rates remain elevated. The goal of this review is to utilize the evidence based medicine approach in searching for the optimal treatment plan of CUA. Despite an array of available treatment options, this article will focus on whether correcting SHPT by parathyroidectomy and the utilization of vitamin D analog therapy helps improve CUA survival rate in dialysis patients. The clinical question, "Does correcting secondary hyperparathyroidism by parathyroidectomy or using an IV vitamin D analog therapy help improve the survival rate in dialysis patients who suffer from calcific uremic arteriolopathy?" is formulated.

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CUA Literature Matrix

Investigators	Year	Class	Sample Demographics	Treatment of CUA	Mention of Vit D Analog	Outcomes	Comments
Yeh[24]	2006	D	1 case: 42yof w/ SHPT, CUA at bilateral lower legs	Total parathyroidectomy (PTX) w/ autotransplantation of parathyroid tissue to the L forearm	Y	Pain improved, CUA healed, Ca/PO4/PTH level imprv post-op. But SHPT recurred 15 mos post-op	PTX is useful mgm't for CUA, but regular f/u of PTH level & imaging studies of possibly residual parathyroid tissues is important.
Don[10]	2003	D	2 cases: Case 1: • 56yoaaf • Proximal CUA • Ca wnl, PO4: 7.5, Alb: 3.2, iPTH: 1044 Case 2: • 51yowf • Distal CUA • Ca wnl, PO4: 11, Alb: 3.4, iPTH: 247	Combo tx strategy: • Change PO4 binder to non-Ca based • ↑HD tx freq from 3x/wk to 5x/wk • ↑Ca conc in dialysate from 2.5 to 1 mEq/l • Vit D analog (paricalcitol)was used in 1 case w/ iPTH >1000 pg/ml, no Vit D usage in another w/ iPTH 247	Y	Both CUA was resolved in ~6 months.	Since combination tx is used, it's difficult to isolate a single strategy that contributes to the outcome.
Wilmer[1]	2002	R			Y	Role of Vit D to the development of CUA remains controversial. But overuse of Vit D analog may result in adverse effect.	PTX promotes wound healing & short term mortality but long-term benefits are largely unknown.
Russell[23]	2001	D	One case: 73yowm HDx3yr	D/C Ca base PO4 binder, switched from Calcitriol to paricalcitol, incr HD time to 6x/wk	Y. Con't on Vit D but changed from Calcitriol to paricalcitol.	Significant healing of the lesions, near-total healing in 1 yr.	

CUA Literature Matrix

Investigators	Year	Class	Sample Demographics	Treatment of CUA	Mention of Vit D Analog	Outcomes	Comments
Kang[16]	2000	D	16 cases (14f, 2m; age 39-70).	PTX & other conventional tx.	Y	Median survival t: PTX grp:14.1mo, nonPTex grp: 6.1mo.	PTX cannot be recommended routinely in all patients, unless severe hyperparathyroidism mandates intervention.
Duffy[20]	2006	D	15 cases w/ proximal & distal CUA: 6 underwent PTX, either subtotal or total, 9 meds controlled	Subtotal & Total PTX	N	Median survival: 39 mos in PTX group vs. 3 mos in meds group	Pts w/ CUA from SHPT should be referred promptly for PTX to promote short-term wound healing & long term survival.
Nunley[3]	2006	R	Narrative Review	PTX, along w/ other tx options, are reviewed	N		PTX may show therapeutic benefit to some but not all. Only a few studies are able to show a decrease in mortality rate in pt undergone PTX.
Ghacha[18]	2006	D	1 case 40yom, CUA @ upper & lower limbs	PTX	N	CUA @ upper limbs healed completely, those in lower limbs showed marked improvement	Response to any therapeutic option is never assured.
Bardsley[19]	2005	D	3 cases: 2 68yof, 1 62yof All with calf CUA All have SHPT	Subtotal PTX	N	2 survived & CUA healed in 6 & 10wks, 1 died post-op day 7.	Option of PTX as tx of CUA should be considered

CUA Literature Matrix

Investigators	Year	Class	Sample Demographics	Treatment of CUA	Mention of Vit D Analog	Outcomes	Comments
Wang[9]	2004	D & R	1 case: 30yof	Medical PTX, & low Ca dialysate bath	N	CUA healed in 2 mos	Medical PTX and low Ca dialysate is recommended to treat early CUA.
Arch-Ferrer[2]	2003	D	35 pts identified at the author's institute. Mean age: 54+/-15yr, 57%aa, 74%f.	PTX	N	Better survival rate in PTX group (80 mo vs 35 mo)	PTX may provide pain relief & ulcer healing, but not all surgical pts survive the dz.
Oh[21]	1999	D	5 cases: age from 40-54yo; 4f, 1m;4 white, 1 hispanic; 3 proximal, 2 distal CUA	PTX Non-PTX group: no details on meds tx besides wound care, surgical debridement, & narcotics for pain	N	Survival rate: PTX group: 1 mo & 3 mo; non-PTX group: 4mo, 6mo, still alive	Benefits of PTX is inconclusive. The rarity of the dz makes it difficult to study tx in any prospective fashion.
Coates[15]	1998	D	16 cases (13f, 3m; age 35-78). 6 w/ SHPT.	PTX	N	Survival: 1/5 in PTX group (ulcer free for 4 yrs), 1/11 in non-PTX group (ulcer free for 18 months).	The study emphasized the dismal prognosis and current lack of effective tx for this condition.
TÖRÖK[22]	1995	D	1 case: 44yof, Ca wnl, PO4 slightly ↑, iPTH↑↑, distal CUA	PTX	N	Ulcers healed after PTX but remission of CUA 2 yr after PTX.	Prognosis, along w/ understanding of etiology & pathogenesis of CUA, remain poor.
Hafner[14]	1995	R	Literature review of 104 cases	PTX	N	Survival: 38/58 w/ PTX vs 13/37 w/o PTX	Only a randomized control prospective trial trial can establish the value of PTX in CUA
Khafif[4]	1990	R	Narrative Review	PTX along w/ other tx options, are reviewed	N		PTX is highly recommended for pt w/ CUA who has SHPT

Searching for the Evidence

A literature search was performed utilizing the 4S approach according to Haynes and colleagues (13). At the top of this hierarchy is System. The Clinical Evidence and National Guideline Clearinghouse database was searched. One result from the National Kidney Foundation's Kidney Dialysis Outcome Quality Initiative (K/DOQI) guideline was generated from the National Guideline Clearinghouse database. However the focus of this result is on vascular calcification instead of the more specific CUA that was being searched. The next ranks of hierarchy consist of Synopses and Syntheses. EBM Reviews, ACP Journal Club, Cochrane, and DARE under OVID were searched. No systematic review pertaining to this clinical question was available. The last step in the 4S approach is Studies. OVID Medline, CINHAL, and the PubMed database was searched. Sixteen articles pertaining to the clinical question were generated under the Medline database. However these were primarily review articles and case studies. High quality primary research studies are lacking. Results from CINHAL are mostly diagnoses articles pertaining more to nursing professionals. One hundred and sixty two results were generated under PubMed. However PubMed was difficult to shift through and most of the findings were irrelevant to the clinical question. The following keywords were used throughout the searching process: calciphylaxis, calcific uremic arteriopathy, nephrocalcinosis, systematic calcinosis, metastatic calcification, cutaneous necrosis, uremic gangrene syndrome, ischemic tissue necrosis; vitamin D, calcitriol, paracalcitol, and doxercalciferol.

All primary research studies located pertaining to this clinical questions are case reports. The total number of cases in each study ranges from one to sixteen. The quality of these studies ranges from neutral to negative or poor due to study design, sample sizes, and lack of statistically significance. The review articles are mostly narrative reviews with only one systematic review located.

Literature Review

Treatment with Parathyroidectomy

Some earlier studies warranted parathyroidectomy as the essential treatment in CUA. Khafif and colleagues concluded in his review article that "It is strongly urged that any time cutaneous calciphylaxis is noted in a patient with chronic renal failure, or pulmonary calcification is identified in a patient with hyperparathyroidism, a total parathyroidectomy be carried out with autotransplantation of one gland in the forearm." (14). The rationale behind this conclusion is to eliminate the sensitizer and the challenger in the suggested inflammation process, a theory developed by Seyle and colleagues.

However, recently published studies do not show a definite correlation between correcting SHPT and CUA as earlier studies did. Although some studies show improvement in survival rate after parathyroidectomy, improvement in survival is not statistically significant. Survival improvement is limited since prognosis of this condition is poor. Recent studies indicate that the overall survival rate for CUA is approximately 1 to 5 years or 45% and 35% respectively (3). Furthermore, a series of interventions, including wound management and change in medications were usually adopted simultaneously as part of the treatment package. Therefore it is challenging to isolate any single treatment plan and its contributions to the improvement in survival rate.

In a systematic review by Hafner and colleagues, a total of 95 cases were reviewed, 58 of these underwent parathyroidectomy after CUA diagnosis. Two thirds of this group (38 out of 58) survived compared with one third (13 of 37) of the patients who did not undergo parathyroidectomy (p=0.007, n=95). Distal CUA was indicated to have a higher survival rate than its proximal counterpart (40 of 53 versus 11 of 42) (15). Limitations of the Hafner review included that an array of treatment options were adopted in the subjects, and there was no control of the auxiliary treatment options since it was a retrospective review. Hence the improvement in survival rate in the parathyroidectomy group may not be fully credited to parathyroidectomy alone.

Case studies conducted by Arch-Ferrer, Coates, Kang, Duffy, and their colleagues all show improvement in short term survival after parathyroidectomy (2,16,17,21). In the study by Arch-Ferrer, 35 patients were identified at the author's institution from 1993 to 2001. Seventy four

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percent were female. Sixty six percent of this group underwent surgical parathyroidectomy to varying extents. They showed improvement in serum calcium, phosphate, and PTH values (P<0.5) post surgery and had a longer median overall survival (80 months) than non-surgical patients (35 months) (2).

Coates and colleagues investigated 16 cases that involved 13 females and 3 males, from 35 to 78 years of age, who were diagnosed with CUA from 1985 to 1996 (16). All of the patients had an elevated calcium and phosphate product in the past and all had elevated PTH either at presentation or in the past. However, in some cases, skin lesions developed with normal calcium phosphate product and PTH level when CUA was diagnosed. Five patients underwent parathyroidectomy as part of the treatment plan of CUA, 3 other patients underwent parathyroidectomy to correct SHPT prior to development of CUA. Only 2 patients survived with slow healing of the lesions - one from the surgical group and one from the non-surgical group. The one who underwent parathyroidectomy, despite recurrence of ulceration, remained ulcer-free for 4 years, versus 18 months in the one who did not undergo parathyroidectomy.

In Kang's retrospective case studies, 7 out of a total of 16 patients underwent parathyroidectomy to treat SHPT (17). Only 1 patient survived out of this group. The overall median survival for all patients was 9.4 months. The surviving patient is alive 53 months after diagnosis. The median survival for surgical patients (14.8 months) from the time of diagnosis was favorable but not statistically different from the median survival in nonsurgical patients (6.3 months; P=0.22). Calcium, phosphorus, and PTH levels in the surgical group before parathyroidectomy are significantly higher than the non-surgical group. It is well established that elevated phosphorus and calcium contributes to increased morbidity and mortality (18). This may play a role in the statistical insignificance of survival rate between the surgical and non-surgical groups.

Some smaller case studies also demonstrate similar results as above. Lesions were healed in 6 weeks to 2 years after parathyroidectomy (9,19,20). In a study by Wang, medical parathyroidectomy was used instead of its traditional surgical counterpart. The patient in this study was treated with three injections of local alcohol into the parathyroid glands for medical parathyroidectomy, accompanied with low calcium dialysate treatment during dialysis. Wound pain and skin ulceration associated with CUA improved significantly 2 weeks later (9).

Duffy and colleagues conducted a study to investigate the long-term outcomes in CUA patients who underwent parathyroidectomy (21). Fifteen patients were identified. Nine were treated with medical therapy (bisphosphonates and phosphate binders), whereas 6 underwent parathyroidectomy. Among the 6 surgical patients, 4 underwent subtotal parathyroidectomy, and 2 underwent total parathyroidectomy. After a 80-month follow-up period, the surgical patients had a longer median survival (39 months), compared with the medical group (3 months).

While the above studies show beneficial effects of parathyroidectomy on CUA outcome and survival rate, some other studies suggest otherwise. Five cases were discussed by Oh and colleagues (22). Four of the five patients had SHPT and only 2 underwent parathyroidectomy. One refused the surgery and the other one did not need one by the time CUA was diagnosed due to normal PTH level. The survival time after CUA diagnosis of the surgical group was 1 month and 3 months respectively, compared to 4 months, 6 months, and still alive at the non-surgical group.

Findings in the case study by Torok showed that although ulcers of the study subject were healed and she sustained a 2-year symptom-free period after parathyroidectomy, the cutaneous lesions of the lower extremities reappeared, with superficial skin involvement that progressed to deep necrotic lesions extending down to the muscular fascia (23). She was diagnosed with tertiary hyperparathyroidism. Since residual parathyroid gland was unable to locate, another parathyroidectomy was not an option. This time both systemic and local treatment failed to arrest the slow progression of the ulcerative cutaneous lesions.

Treatment with Vitamin D Analog Therapy

Only 2 case series mention vitamin D analog therapy in the treatment of CUA. However neither could isolate

the beneficial effects of vitamin D therapy alone to CUA. In a case presented by Russell, the treatment package entailed switching phosphate binder to a calcium-free one (Sevelamer hydrochloride (Renagel®)), increasing duration of dialysis treatment, and replacing a more calcemic vitamin D analog calcitriol (Calcijex ®) with the active vitamin D3 analog paricalcitol (Zemplar ®) (24). Vitamin D therapy was slowly weaned afterwards. Although serum intact PTH trended up subsequently to above normal limit after discontinuing paricalcitol, the patient's phosphorus and calcium level improved to normal levels gradually, and significant healing of the lesions was noted at 8 months following diagnosis, with near-total healing by 12 months.

Treatment with Combination Therapies

A combination of therapies was employed to correct CUA in two cases discussed by Don and Chin (11). Both cases had similar demographic background. Case 1 was diagnosed with proximal CUA while case 2 was diagnosed with distal CUA. The PTH level in case 1 was greatly elevated but was normal in case 2. A combination of treatment utilized was similar to the one mentioned above by Russell. Although PTH in case 2 subsequently trended up to above normal, only case 1 was given vitamin D therapy. Paricalcitol was used in this case. CUA was resolved in both cases in 6 and 7 months respectively.

Yeh and colleagues described a case with a 42-year-old female CUA patient who underwent total parathyroidectomy with autotransplantation of the parathyroid tissue to the left forearm (25). The patient was treated with a phosphate binder and vitamin D3 continuously. The pain and wound area improved following surgery in combination with skin grafts and hyperbaric oxygen therapy. Serum PTH level improved significantly post operation. However, SHPT recurred 13 months after surgery.

Due to the lack of studies that focus on the use of vitamin D therapy alone as a treatment option for CUA, a direct association of the beneficial effects of vitamin D in treating CUA could not be made. However, as illustrated in the previous sections of this article, the correction of serum calcium and phosphorus levels significantly improve CUA outcomes. Therefore, the use of vitamin D, especially the less calcemic option, paricacitol, to aide in the correction of SHPT, in combination with other treatment options, seems to be a more conservative approach.

Other Speculated Causes of CUA

Although the pathogenesis of CUA is still elusive and only a few studies are able to suggest a mechanism that may lead to the development of CUA, several reports indicate some speculated risk factors for the syndrome. These include obesity, elevated serum phosphorus and calcium level, the use of Warfarin, protein C and protein S deficiency, vitamin K deficiency, malnutrition, rapid weight loss, and lack of natural calcification inhibitors, such as matrix GLA protein(1, 26). Since the goal of this article is to focus on SHPT and CUA, details of these potential causes are not further elaborated on in this article. These are deduced causes based on retrospective case studies. A complete explanation of why CUA develops in some patients but not others with similar risk factors still remains intangible.

Other Speculated Causes & Risk Factors of CUA:

- Caucasian race
- Females
- DM
- HIV+
- Obesity
- Malnutrition
- Elevated serum Ca & PO4
- Secondary Hyperparathyroidism
- Usage of Warfarin
- Protein C and/or Protein S deficiency
- Vitamin K deficiency
- Inflammation
- Lack of Calcification Inhibitors (i.e. matrix GLA protein, osteopontin, fetuin-alpha2)

Additional Treatment Options for CUA

Treatment of CUA is mainly supportive. Early detection of the condition allows the avoidance or removal of potential sensitizers and challengers. Normalization of serum calcium and phophorus levels through the prescribed nutrition plan and medications is crucial. Aggressive wound care with careful debridment,

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hyperbaric oxygen therapy and prednisone is commonly adopted. Some studies demonstrate promising results following the use of sodium thiosulfate. The use of antibiotics to control infection and narcotics to control pain is also widely reported as part of the supportive treatment of CUA (1, 22, 27).

Treatment Options for CUA:

Supportive:	Wound Healing (Hyperbaric O2, Debridment)
Medical:	Phosphate binder (non-Ca based) Antibiotics for infection Steroids Necrotics for pain control IV Sodium Thiosulfate IV vitamin D analog therapy
Surgical:	Parathyroidectomy

Conclusion

Understanding of the pathogenesis and cause of the CUA process is not easy. Most suggested theories are hypothetical at best, based on single retrospective case reports. No single theory is sufficient to explain all cases. The failure to understand the inherent and underlying pathophysiologic factors of this disease entity has led to the current suboptimal treatment and a poor long-term prognosis. Few researchers will argue with the importance of local wound care, but treatment for SHPT remains controversial in treatment of CUA. Parathyroidectomy may result in pain relief and ulcer healing. However, not all surgical patients survive their disease. Direct association of the usage of vitamin D therapy alone in CUA is weak but the efficacy in the usage of vitamin D therapy in treating SHPT is undeniable. The evidence answering this clinical question is weak and is mostly due to the lack of a specific study, poor study design, and small sample sizes of the studies.

A common denominator of the conclusion of the articles reviewed thus far is the quest for a prospective, randomized controlled trial to further study the pathogenesis and hence the best treatment of CUA.

Implications for Clinical Practice

More high quality research is definitely warranted in the pathogenesis and treatment strategy of CUA. As an aside, it may be interesting to investigate whether C-reactive proteins have any correlation with CUA.

Until strong evidence in this area arises, practitioners need to treat CUA based on their best clinical judgment according to their past experience and on a case by case basis. Elimination of speculated risk factors one at a time may be the best treatment approach currently due to the lack of a conclusive understanding of the syndrome.

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