Presentation and Treatment of Calcific Uraemic Arteriolopathy

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Background

Calcific Uraemic Arteriolopathy (CUA, Calciphylaxis) is a rare disorder characterised by soft tissue calcification. The uraemic environment is uniquely permissive to vascular calcification due to perturbations in mineral homeostasis, uraemic toxins, loss of calcification inhibitors, and oxidative stress. While large vessel calcification is radiologically identifiable in 80-100% of dialysis patients, small vessel calcification is often occult, but can become overt as CUA.

CUA causes **painful** lesions with induration and *levido reticularis*, often leading to **necrosis**, ulceration and secondary infection. Those with renal failure, poorly controlled Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD), diabetes mellitus and treatment with **vitamin K antagonists** such as warfarin are most at risk. Histopathologically, **small and medium sized arteries** demonstrate medial calcification and intimal hyperplasia, endovascular fibrosis and thrombosis, resulting in tissue ischemia and necrosis.

CUA in patients with kidney failure carries a **poor prognosis**, with 1-year mortality as high as 55%.[1] However, emerging evidence suggests improved outcomes with the use of Sodium Thiosulphate (STS) or Calcimimetics.[2]

Methods

Data: In this retrospective cohort study, we identified all patients diagnosed with CUA at our centre between 1st January 2009 and 31st December 2013. We included all prevalent dialysis patients (haemodialysis and peritoneal dialysis) at Addenbrooke's Hospital, Cambridge, and its satellite dialysis centres.

CUA cases were identified from electronic health records and pathology reports, and verified with the responsible nephrologist. Demographic data, dialysis modality and vintage, prescriptions, biochemical parameters (albumin-corrected calcium, phosphate, parathyroid hormone (PTH) alkaline phosphatase (ALP), HbA1C, creatinine, C-reactive protein (CRP)) and haematological indices (haemoglobin, white cell count, platelets) and date of death were abstracted from electronic health records.

Analysis: Data are shown as mean SD or median (IQR) as appropriate. Comparisons of parametric and non-parametric variables were made by Student's T-test or Mann-Whitney U-Test respectively, and comparison of proportions were made with two-sided Fisher's exact test.

All analyses were carried out using Stata SE release 13.1.

Results

Patients

Population: During the 5-year study period, 2,088 patients received renal replacement therapy at our hospital and its satellite units. Of these, 289 received peritoneal dialysis at some point during the study.

Cases: We identified 5 cases of CUA during the study period. One patient was diagnosed at dialysis initiation; one patient developed CUA immediately post-transplantation. Cases are summarised below:

Case number	1	2	3	4	5	Mean/Median
Age (yrs)	75	69	46	64	73	66 ± 12
Gender	Female	Female	Female	Female	Female	
Vintage (months)	22	3	95	0	47	41 ± 40
Kt/V	2.06	3.8	1.72*	1.6	1.75	2.2 ± 0.9
URR (%)	73	71	79*	-	78	74.4 ± 3.8
Dialysis frequency	3/wk	3/wk	3/wk	3/wk	3/wk	3/wk
Primary disease	Htn	DN	NC	LN	Unknown	-
Comorbidities	-	PVD, HF	-	-	PVD, IHD	-
Gout	+	-	-	-	-	-
Diabetes	-	Insulin	-	-	-	-
BP drugs	0	2	1	0	0	-
CRP	34	82	52	45	11	45 ± 26
Calcium	2.3	2.22	2.39	2.19	2.79	2.38 ± 0.24
Phosphate	1.76	1.48	1.68	1.16	1.24	1.46 ± 0.26
PTH	414	172	18	37	180	172 (37 - 180)
Phosphate binders	Calcium carbonate	Calcium acetate	Sevelamer	Calcium acetate	Calcium acetate	-
Anticoagulation	Warfarin	Warfarin	Warfarin	Warfarin	-	4/5
Post diagnosis management and outcome						
STS	Yes	Yes	Yes	-	Yes	-
Cinacalcet (mg/d)	18	30	-	30	30	-
Anticoagulation	Dabigatran	Dalteparin, Dabigatran	-	Dabigatran	-	-
Phosphate binders	Sevelamer	Sevelamer	Sevelamer	Sevelamer	Sevelamer	-
Antimicrobials	-	-	Yes	-	-	-
Other	PTX	-	Pamidronate	-	PTX	-
Survival (mths)	30	7	23	51	42	30 ± 17
Cause of death	-	Brain stem infarct	-	-	-	

*** Patient 3 presented immediately post transplant – adequacy values represent last pre-transplant values. URR- urea reduction ratio; BP- blood pressure; CRP- C reactive protein; Htn – hypertension; DN – diabetic nephropathy; NC – nephrocalcinosis; LN – lupus nephritis. PVD – peripheral vascular disease; HF – heart failure; IHD – ischemic heart disease; PTX – parathyroidectomy; PTH- parathyroid hormone**

Cases

Case 1: Warfarin (4 years) for recurrent venous thromboembolism. Lesions on infra-umbilical abdominal wall – histological confirmation. On Cinacalcet for 1 year preceding diagnosis for severe hyperparathyroidism.

STS administered for 3 months, then received parathyroidectomy. Full recovery, remains well.

Cases

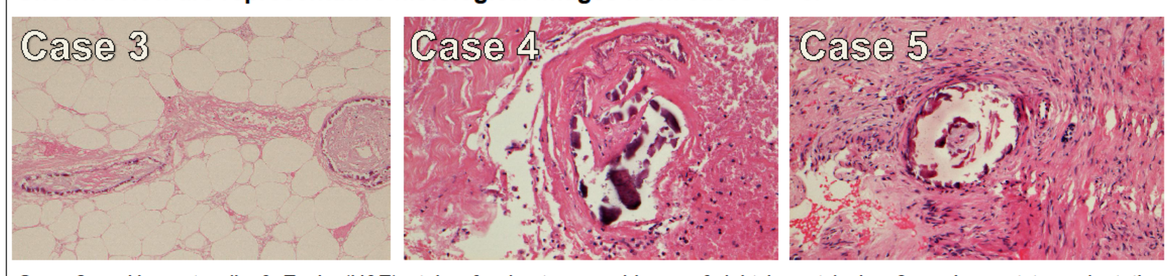
Case 2: Complicated type II diabetic female, Warfarin for 30 months pre-diagnosis for recurrent venous thrombo-embolism. Abdominal wall lesions with cutaneous infarction, histological confirmation.
Dalteparin converted to Dabigatran due to alopecia. STS poorly tolerated (nausea, only 5 doses). Death due to basilar artery thrombosis.

Case 3: Post transplant hypercalcaemia coincided with lesions over breast and upper arms. Warfarinised for recurrent venous thrombo-embolism for 5 years pre-transplant. STS 3 x weekly post transplant. Ongoing hypercalcaemia necessitated IV bisphosphonate. Lesions did not resolve and breast lesions were ultimately resected.

Case 4: Female with SLE, positive lupus anticoagulant, nephrotic, previous PE, thus on warfarin for 5 years pre-diagnosis. Presented at dialysis initiation with abdominal wall lesions. Lesions resected due to intolerable pain. Cinacalcet eventually withdrawn due to PTH over-suppression.

Case 5: Bilateral amputee (PVD), hypercalcaemic, secondary hyperparathyroidism, lesions on both lower limb stumps. Treated with STS for 3 months pending parathyroidectomy. Has made a good recovery.

Shown below are representative histological images from cases 3 – 5.



Case 3 – Haematoxylin & Eosin (H&E) stain of subcutaneous biopsy of right breast lesion 6 weeks post transplantation demonstrating vessel wall calcification, intimal hyperplasia and sclerosis. **Case 4** – Abdominal wall subcutaneous biopsy from case 4 at diagnosis, demonstrating calcification of an arteriole with luminal debris. **Case 5** – Subcutaneous tissue from the right thigh of patient 5 demonstrating circumferential calcification and intraluminal debris, with perivascular inflammation and fibrosis.

Warfarin and CUA

Known risk factors for CUA include renal failure, disordered mineral metabolism, diabetes mellitus, and treatment with vitamin K antagonists. All 5 cases reported here had ESRD; only one was diabetic, and two had parathyroidectomy-requiring hyperparathyroidism. However, 4 of 5 cases had received treatment with warfarin.

	Warfarin	No Warfarin	Total
CUA	4	1	5
Control	138	1945	2083
Total	142	1946	2088
Risk	2.8%	0.05%	0.2%

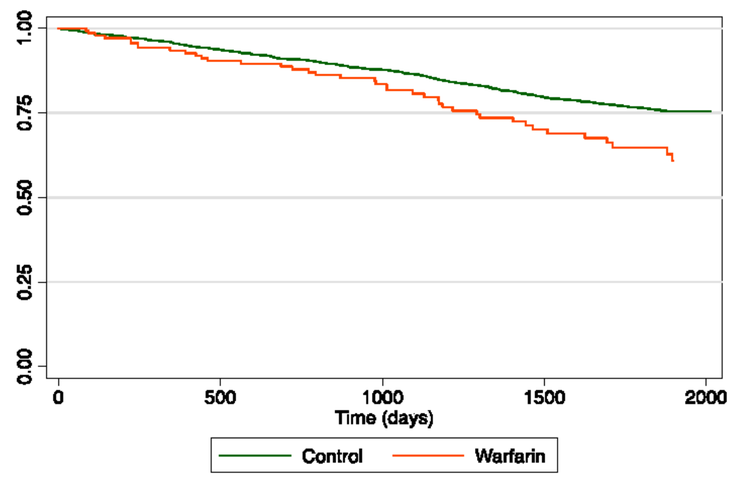
Odds Ratio = 56
(95%CI 17 – 190)

p = 0.0001

Therefore in our cohort, warfarin use conferred a considerable risk of developing CUA.

Further, given that vitamin K antagonism creates an environment permissive to general vascular calcification, and since both CUA and large vessel calcification are associated with increased risk of cardiovascular death, we carried out an exploratory survival analysis in warfarin-treated versus untreated patients in our cohort.

Kaplan Meier Survival Curves of Warfarin-Treated Patients versus Controls



Patients receiving warfarin therapy were at an increased risk of death compared to controls. In a multivariate model adjusted for age, dialysis vintage, modality, gender and the use of warfarin, the only significant associations with mortality were warfarin use (HR 1.6, 95% CI 1.15 – 2.19, p = 0.005) and patient age.

Conclusions

We describe 5 cases of CUA, and identify a strong association with warfarin use. Although the number of cases is small, our findings support the hypothesis that vitamin K antagonism promotes vascular calcification.

Our observation that discontinuation of warfarin, and the institution of multimodal therapy including STS, calcimimetics and calcium free phosphate binders may lead to resolution suggests that warfarin-associated CUA may carry a better prognosis than CUA occurring in the absence of warfarin therapy.

Our data showing reduced survival in warfarin-treated patients should be interpreted with caution as we have not been able to account for confounding by indication, and our study is open to all the limitations of retrospective cohort studies.

References

1. Fine A, Zacharias J. Kidney Int 2002; 61, 2210-2217
2. Zitt E et al. Nephrol Dial Transplant 2013; 28, 1232-1240

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