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Uraemic tumoral calcinosis in patients on haemodialysis in the renal unit at Dr George Mukhari Hospital, Pretoria

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Abstract

Objective. Uraemic tumoral calcinosis refers to metastatic calcifications that occur rarely on the extensor surfaces of joints in patients undergoing long-term haemodialysis. The aim of the study was to assess the incidence of uraemic tumoral calcinosis in participants undergoing haemodialysis and to investigate any relationship that might exist between the development of uraemic tumoral calcinosis and the length of time on dialysis.

Design. Twenty-four of the 25 patients on haemodialysis at the time of the study underwent radiographs of their shoulders and hips to look for calcinosis, which were then read by the researcher and two independent readers to assess for calcinosis.

Study setting. Dr George Mukhari Hospital, Pretoria.

Results. Eight per cent ($N=2$) of participants were found to have asymptomatic calcinosis of the hips. No relationship to length of time on dialysis was found.

Conclusions. The study was constrained by a small sample size but the presence of calcinosis in 8% of the participants indicates that an extensive study of a larger sample could prove to be useful in determining the true incidence of uraemic tumoral calcinosis in the region. Long-term follow-up could provide more information on the development of calcinosis and length of time on dialysis.

Introduction

Tumoral calcinosis may be defined as metastatic peri-articular calcifications that can be found in a wide variety of conditions such as primary hyperthyroidism and connective tissue diseases, as well as an idiopathic form.¹

Uraemic tumoral calcinosis is an uncommon occurrence in patients with chronic renal failure who are on long-term haemodialysis therapy, and falls within the broad definition of tumoral calcinosis.¹

The disease is usually asymptomatic but can present with complications such as impairment of mobility, nerve compression, ulceration of the overlying skin and bony erosion.¹

If the radiologist is unfamiliar with the radiological patterns of tumoral calcinosis or disease processes that mimic the condition, then diagnosis and treatment might be delayed or the patient may be subjected to unwarranted invasive procedures.²

Literature review

Metastatic calcifications may have benign or malignant causes.³ Uraemic tumoral calcinosis is known to occur in patients with chronic renal failure undergoing haemodialysis and is the most common cause of metastatic peri-articular calcifications.³ The aetiology is multifactorial and awareness is important since the condition is progressive.¹ The disease is uncommon and current prevalence is not well known but a frequency range of 0.5 - 3% has been reported.⁴

The pathogenesis is not fully understood but significant disturbances of calcium and phosphate homeostasis can result from chronic renal disease. Among these disturbances are decreased phosphate excretion,

which leads to decreased calcitriol synthesis and hyperparathyroidism.⁵ Decreased calcitriol leads to decreased intestinal absorption of calcium, which further stimulates hyperparathyroidism, eventually leading to autonomous hyperparathyroidism that results in hypercalcaemia.⁶

Hyperphosphataemia and $\text{Ca} \times \text{PO}_4$ product greater than 60 - 75 and hyperparathyroidism are thought to be strong risk factors.^{3,4} High dialysate calcium concentrations are also implicated.^{1,4} Studies also suggest that uraemic tumoral calcinosis occurs more commonly in patients on haemodialysis for more than 3 years.⁸

Patients with uraemic tumoral calcinosis may be asymptomatic or present with joint mobility impairment.⁹ Nerve compression can occur with large 'tumours' and, less commonly, ulceration of the overlying skin with discharge of milky white fluid.¹ Uraemic tumoral calcinosis may induce a systemic inflammatory response presenting as a pyrexia of unknown origin.⁷ The extensor surfaces of joints are usually involved, with the hip, shoulder and elbow (in order of decreasing frequency) commonly affected.⁸

Radiologically, multiple large lobulated homogenous calcifications are noted in the soft tissue around the joint, with the joint spaces preserved.¹ Lesions may vary in size from 2 - 10 mm.⁸ No bone, muscle or visceral invasion is usually noted,¹ but some cases report a degree of bone erosion in extensive calcinosis.⁸

The differential diagnosis for soft tissue calcifications should include idiopathic tumoral calcinosis, collagen vascular diseases (scleroderma, rheumatoid arthritis, systemic lupus erythematosus and dermatomyositis), myositis ossificans, metabolic causes (hyperparathyroidism) and neoplasms (osteosarcoma and chondrosarcoma).^{1,4} These diseases can usually be differentiated radiologically from uraemic tumoral calcinosis and a biopsy is rarely warranted.

Treatment options used in patients with uraemic tumoral calcinosis are usually aimed at correcting the underlying cause. Relief may be achieved by surgical resection in patients presenting with symptoms, but excision is usually incomplete and recurrence is common.^{4,8} Total or subtotal parathyroidectomy has also been shown to be effective in some patients, emphasising the important role of secondary hyperparathyroidism in patients on haemodialysis.¹⁰ This treatment option remains controversial, with other authors arguing that it has not been shown to be effective in the majority of patients and, in some cases, progression of calcinosis was noted following this method of treatment.¹¹

Medical interventions are aimed at correction of $\text{Ca} \times \text{PO}_4$ product. Induction of a negative Ca balance by increasing the number and duration of haemodialysis sessions with a low dialysate Ca concentration has been reported to bring about a reduction of the masses.⁶ Sodium thiosulphate may improve solubility and mobilisation of calcified masses but needs further investigation. Tumoral calcinosis often resolves after successful renal transplantation, which is the definitive therapy for this condition.⁶

The disease is progressive. It is therefore vital that the prevalence of uraemic tumoral calcinosis in the renal haemodialysis unit of Dr George Mukhari hospital be assessed so that appropriate measures can be taken for its prevention, such as decreasing the calcium concentration in dialysis solutions or increasing duration of haemodialysis.

Aim

The study was a preliminary investigation of the incidence of uraemic tumoral calcinosis in a sample of 25 patients known to be on renal haemodialysis at the Dr George Mukhari Hospital (GMH) so as to determine any relationship that might exist between the development of uraemic tumoral calcinosis and the length of time on dialysis, and to suggest interventional and preventative methods to reduce development and progression of the condition in any of the patients found to be affected.

Methodology

A prospective study was conducted on 25 patients on the haemodialysis programme at the time. One patient subsequently refused radiography. Twenty-four participants had radiographs taken of their hips and shoulders. One participant, with clinically palpable nodules of both wrists, had radiographs of both wrists in addition to hips and shoulders. The radiographs were then assessed by the researcher and 2 consultant

Table I. Percentage of patients in each period of dialysis

Period of dialysis	N (%)
0 - 12 months	5 (20)
13 - 24 months	6 (24)
25 - 36 months	6 (24)
37 - 48 months	5 (20)
49 - 60 months	1 (4)
61 - 72 months	0 (0)
73 - 84 months	1 (4)
Missing	1 (4)
Total	25 (100)



Fig. 1. Calcifications on the extensor surface of both hips in a patient on haemodialysis for 12 months.

Table II. Assessment of calcinosis in hips, shoulders and wrists by each reader and researcher

Reader	Calcinosis					
	Hips		Shoulders		Wrists	
	Yes	No	Yes	No	Yes	No
Researcher	8%	88%	96%	96%	100%	100%
Reader 1	8%	88%	96%	96%	100%	100%
Reader 2	4%	92%	96%	96%	100%	100%

N=24



Fig. 2. Small area of calcification on the extensor surface of the left hip in keeping with calcinosis in a patient on haemodialysis for 15 months.

radiologists in the radiology department at GMH, for the presence of calcinosis.

Bias

All patients on haemodialysis were included in the study, except for one who subsequently refused to be radiographed. All radiographs were read by the researcher and 2 independent readers to avoid introduction of any form of bias. A discrepancy arose between the readers regarding findings on the radiographs of one participant, for which case only a third reader was involved.

Validity

Validity can be defined as the degree to which a test measures what it is supposed to measure.¹² Radiographs are the best method of detecting, localising and diagnosing soft-tissue calcifications in patients.⁸ All participants had radiographs taken of their shoulders and hips (the most common sites for uraemic tumoral calcifications) to look for soft-tissue calcifications.

Reliability

The reliability of a research instrument concerns the extent to which the

instrument yields the same results on repeated trials.¹² As radiological images were used to assess the radiological patterns of tumoral calcinosis, the researcher used a reliable and validated instrument of measurement.

Results

Data were assessed using the Chi Square Test Statistical Package for the Social Sciences (SPSS) version 15 and Statistical Analysis System (SAS) version 9.2.

A sample of 25 patients on haemodialysis in the renal unit at GMH were assessed for the study. One patient did not present himself for radiographs and was excluded from the analysis. Of the 24 participants comprising the sample, 60% were male and 40% female. The range of the dialysis periods for the 25 patients is shown in Table I.

Two participants were found to have radiological evidence of calcinosis. Of these, one participant was on dialysis between 0 - 12 months (Fig. 1) while the other participant was on dialysis for 13 - 24 months (Fig. 2). Only one participant (4% of the sample) was found to have nodules which were detected in both wrists. The other 96% had normal clinical examinations of the joints. Assessment of calcinosis is illustrated in Table II (24 participants).

Only one participant had radiographs of both wrists because nodules were found on them during clinical examination, but no calcinosis was found radiologically. A discrepancy was found between Reader 1 and Reader 2 regarding the presence of calcinosis in one patient. A third reader was then asked to assess the relevant radiograph to improve the validity of the study, and she concurred with Reader 1.

Chi-square analyses indicated that there were no significant differences between the variables:

- gender and length of period of time on dialysis ($p>0.78$)
- presence/absence of nodules and period of time on dialysis ($p>0.68$)
- presence of calcinosis and length of period of dialysis ($p>0.92$).

Discussion

The small sample size means that the results of the study may not be statistically significant. However, since this study was the first at GMH, it allows for ancillary treatment of participants who were found to have uraemic tumoral calcinosis, and it allows for further research.

The findings reflect that the prevalence of uraemic tumoral calcinosis in the population of patients attending haemodialysis at the renal unit of GMH during December 2007 was 8%, with the literature reporting the range to be 0.5 - 3%.⁴ No correlation was found between the length of time on dialysis and the incidence of calcinosis in this research setting. The literature suggests that uraemic tumoral calcinosis occurs more commonly in patients on haemodialysis for more than 3 years.⁸ Interestingly, both participants found to have calcinosis in our study had been on haemodialysis ≤ 24 months while none of the patients on haemodialysis ≥ 36 months were found to have been affected. None of the studies referred to the correlation between uraemic tumoral calcinosis and length of time of renal failure. Males and females were equally affected by calcinosis, so no gender predilection appears to exist.

The clinical presence of nodules did not correlate with the presence of calcinosis either, as the one participant with nodules did not have calcinosis. The nodules in this patient represented soft-tissue swellings, probably related to previous catheterisation of vessels in the wrists. Both patients with calcinosis did not have any palpable nodules and were found to have involvement of the hips, which is the most common site of involvement noted in the review of the literature.⁸

The results of this study were forwarded to the renal unit at GMH so that appropriate interventions could be instituted, i.e. increased duration and frequency of dialysis and changes in dialysis solution, to benefit those participants affected by calcinosis.

Conclusions and recommendations

The study was the first of its kind conducted at our institution. The small sample size implies that the study might not be statistically significant, but it opens the door to further research in this field. Among the questions raised by the study are the following:

- Will a larger sample size involving participants from other hospitals in the region provide a better reflection of the incidence of uraemic tumoral calcinosis in our region?
- Will long-term follow-up of our participants provide a better understanding of the relationship between development of calcinosis and length of time on dialysis?
- What is the underlying cause of uraemic tumoral calcinosis in our participants and what measures should be implemented to treat them?

The results of the study have been presented to the head of the renal unit, and the following recommendations for implementation were made:

- assessment of the affected participants $\text{Ca} \times \text{PO}_4$ product
- assessment of parathyroid hormone levels
- intervention aimed at correcting the above factors
- regular radiographic follow-up to assess progression/regression of calcinosis
- regular monitoring clinically and radiographically of patients on long-term haemodialysis to allow early detection of calcinosis.

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