

Journal reading

Intern 李思佳

Therapy for calciphylaxis: An outcome analysis

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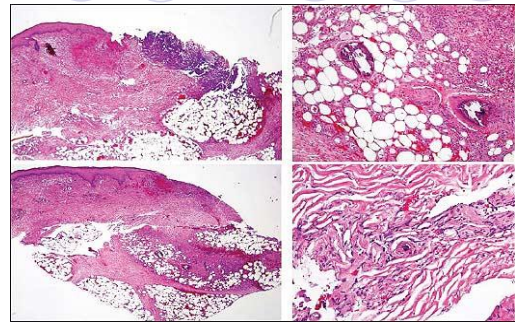
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Introduction

- Calciphylaxis is an **uncommon condition** that occurs in patients with **chronic renal failure** and is associated with **secondary hyperparathyroidism**.
- Calciphylaxis is characterized by **progressive vascular and soft tissue calcifications** and **painful, violaceous skin lesions** (livedo reticularis), which may progress to ischemic skin necrosis, nonhealing ulcers, gangrene, and amputation.



Introduction

- **Sepsis** and **death** occur in approximately **60%** of patients.
- Treatment consists of **local wound care**, including debridement, antibiotics, **lowering of serum phosphate levels** (reduce dietary phosphate to less than 1,000 mEq/24 hours and administer phosphate binders), and **parathyroid resection**.
- The role and timing of parathyroid resection continues to be **controversial**.
- This study analyzes outcome in calciphylaxis patients undergoing **surgical** and **nonsurgical therapy**.

Material and methods

- A search of a parathyroid disease database at the University of Alabama at Birmingham, which was developed by the senior author (AGD), yielded **35 patients** with calciphylaxis treated **between 1993 and 2001**.
- **Patient, disease, and treatment variables** were obtained from the database and from the patients' **medical records**.
- **Patients** or **surviving relatives** were contacted by telephone to determine **outcome**.

Material and methods

- Response to treatment was defined as the **healing of preexisting lesions** and the **development of no new lesions**.
- Paired t-test, chi-squared analyses, and two-tailed Fisher's exact tests** compared patient, disease, and treatment variables, depending on the type of data.
- The **Kaplan-Meier method** was used to develop survival curves and the **log-rank test** was used to determine survival differences.

Results

- Between July 1993 and August 2001, **35 patients** were treated for calciphylaxis.
- The mean age at diagnosis was **54 ± 15 years**.
- In **13 patients** (37%), the **cause** of renal failure was **hypertension**, whereas in **nine** (26%) the cause was **diabetes mellitus**.

Results

- At the time of diagnosis, **29 patients** were undergoing **renal replacement therapy** (hemodialysis in 24 [69%] and peritoneal dialysis in five [14%]) for a median duration of **31 months**, whereas **five patients** (14%) had had a **renal transplant**.
- Symptoms at the time of diagnosis were a **cutaneous ulcer** in **19** (54%), a **cutaneous mass** in **17** (49%), and **pain** in **31** (89%).



Fig. 1. Abdominal ulceration due to calciphylaxis (left) with evidence of how left hip removes the calcification.

Results

Table I. Patient and disease variables by type of treatment

	Surgical (n = 23)	Nonsurgical (n = 12)	P value
Age (yr)	54 ± 13	60 ± 17	0.07
Serum calcium (Ca)	9.5 ± 18.7	8.8 ± 1.0	n.s.
Serum phosphate (P)	6.8 ± 2.3	5.8 ± 1.7	0.06
Parathyroid hormone	1754 ± 2744	462 ± 444	n.s.
Ca-P product	80 ± 20	59 ± 17	<0.01
African-American	14	6	n.s.
Hypertension	9	4	n.s.
Diabetes	7	2	n.s.
Hemodialysis	18	6	n.s.
Renal transplantation	4	1	n.s.
WBC >15,000	5	6	n.s.
Ca × P >70	17	5	0.08
Cutaneous ulcer	10	9	n.s.
Cutaneous mass	12	5	n.s.
Proximal location	13	5	<0.01
History of trauma*	0	3	<0.05
Iron supplements	8	7	n.s.
Corticosteroids	4	4	n.s.
Immunosuppressants	3	3	n.s.
P-binding antacids	11	11	0.06
Oral anticoagulants	7	3	n.s.

*History of trauma to the area of disease.

Results

- Medical therapies included **iron supplementation** in 15 (43%), **corticosteroids** in **eight** (23%), other **immunosuppressants** in **six** (17%), and **phosphate-binding antacids** in **22** (63%).
- Twenty-three patients underwent a **parathyroid resection**. Parathyroid resections included **four glands** and autotransplantation in **six** (17%), **3½ glands** in **seven patients** (30%), and **fewer than 3½ glands** in **four patients** (17%).
- The mean time between diagnosis and surgery was **6 ± 16 weeks**.

Results

- There was **significant improvement** in the postoperative values.

Table II. Pre- and postoperative laboratory values in 23 patients undergoing parathyroid resection (paired t-test)*

	Calcium (Ca)	Phosphate (P)	PTH	Ca-P product
Preoperative	9.5 ± 18.7	6.8 ± 2.3	1754 ± 2744	87 ± 18
Postoperative	7.1 ± 1.8	4.4 ± 2.1	74.6 ± 78.8	26 ± 11
P value	<0.001	0.04	<0.005	<0.001

*Values are mean ± SD.

Results

- After median follow-up of 26 months (range 2 to 90 months):

Table III. Outcome by treatment group

Status	Nonsurgical (n = 12)	Surgical (n = 23)
Dead of disease	6	2
Dead of other causes	3	7
Complete response	0	6
Improvement	0	3
Stable disease	2	2
Worsening	1	0
Lost to follow-up		3

Results

- By two-tailed Fisher's exact test, patients with a cutaneous ulcer ($P = .07$), a proximal lesion ($P = .05$), a history of trauma ($P = .06$), and a white blood cell count of 15,000 or more ($P = .007$) had a worse clinical response, whereas patients undergoing parathyroid resection had a better response ($P = .001$).
- By log rank test, patients undergoing parathyroid resection showed a better median overall survival (80 months vs 35 months), as did patients with a Ca-P product of 70 or more. (why? See next slide)

Results

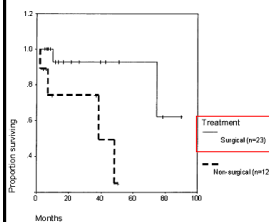


Fig 1. Overall survival for 35 patients with calciphylaxis. Survival was better in patients undergoing surgical treatment (parathyroid resection) (median survival 80 vs 35 months, $P = .01$, log rank test).

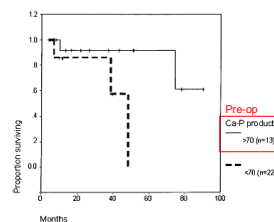


Fig 2. Overall survival curve for 35 patients with calciphylaxis. Survival was better in patients with a Ca-P of 70 or more ($P = .04$, log rank test), possibly because these patients usually underwent parathyroid resection.

Discussion

- We found that a cutaneous ulcer, a proximal location, a history of trauma to the area of disease, and a white blood cell count of more than 15,000 were associated with a worse clinical response to treatment, but not with worse survival.
- Some patients with calciphylaxis who undergo parathyroid resection die of their disease, but patients receiving surgical therapy generally do better than those treated nonoperatively.

Discussion

- A calcium - phosphate product (Ca-P) of 70 or more is seen in many patients with calciphylaxis and may be an indication for parathyroid resection. When Ca-P reaches this level, calcium deposition in soft tissues becomes more frequent.
- In the current study, surgical patients had:
 - elevation of Ca-P when compared with nonsurgical patients (80 ± 20 vs 59 ± 17 [$P = 0.01$]);
 - a better clinical response ($P < 0.001$); and a better overall survival ($P = 0.01$).
- Parathyroid resection lowered the Ca-P product ($P < 0.001$).

Discussion

- Parathyroid resection results in pain relief and ulcer healing.
- There is a strong consensus that parathyroid resection is associated with pain resolution, better healing of ulcerations, and prolonged survival.

Conclusion

- For patients with a Ca-P of 70 or more, we recommend **four-gland parathyroid resection with autotransplantation of parathyroid tissue** to the brachioradialis muscle of the forearm.
- **Early detection** of disease and **debridement of cutaneous ulcers** may also contribute to a better outcome.

Thanks for your attention!!

Cinacalcet (Mimpara®/Sensipar®)

- Cinacalcet is the first of a new class of drugs, the **calcimimetics**. It acts by **increasing the sensitivity of the calcium-sensing receptor to calcium**, thus leading to a **reduction of the parathyroid hormone**, and yet at the same time a **reduction in serum calcium, serum phosphate and calcium phosphate product**.
- In three **randomized, double-blind, placebo-controlled trials** in 1136 dialysis patients with poorly controlled secondary hyperparathyroidism, cinacalcet was shown to **reduce parathyroid hormone** by a median of **48.2–54.1%**, with a concomitant reduction in calcium phosphate product of **14.9–19.7%**.
- The **major side effects** were **nausea** and **vomiting**.



Fig. 1. Abdominal ulceration due to calciphylaxis (left) with evidence of huge left hip tumour-like calcification.



Fig. 3. Complete healing of abdominal ulceration (due to calciphylaxis) and regression of tumour-like calcification following treatment with Cinacalcet.