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CASE REPORT

Non-uremic Calciphylaxis: A Rare and Late Adverse Reaction of Warfarin

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Abstract: ***Background*:** Calciphylaxis is a complex dermatological lesion of micro vascular calcification that is typically presented as panniculitis with gangrenous painful lesions having uremic and non-uremic causes.

***Case Report*:** We present a case of a 48-year old male with a history of paroxysmal atrial fibrillation and hypertension taking amlodipine 5 mg and warfarin 5 mg daily for the last 26 months. The patient had a 6-months history of painful swelling followed by necrotic skin ulcer over the right leg. His remarkable examination findings were right leg tender ulcer with surrounding erythema and secondary sepsis. His hemogram, metabolic profile and connective tissue diseases work up were unremarkable except leucocytosis and raised inflammatory markers. His local part radiological and skin biopsy findings were suggestive of calciphylaxis.

***Results and Conclusion*:** In our case, warfarin and amlodipine were culprit drugs for the lesion, but Naranjo score (warfarin 7and amlodipine 1) speculate warfarin as a probable adverse reaction of warfarin. The lesion was cured with local wound treatment after discontinuation of warfarin. The physician should be aware of this rare cutaneous disorder of systemic origin for proper management.

Keywords: Non-uremic, calciphylaxis, warfarin, adverse drug reaction, ESRD, TIA.

1. INTRODUCTION

Calciphylaxis is a rare life-threatening condition that presents as painful violaceous patches and ulcerations on various parts of the body due to calcification of the small blood vessels of subcutaneous tissue and dermis, thrombosis of the vessels and skin necrosis. This condition is commonly presented with erythema nodosum, panniculitis, and skin gangrene with purpura or non-healing ulcers [1]. Calciphylaxis is typically associated with end-stage renal disease (ESRD), although only 1-2% of all ESRD patients develop calciphylaxis [2]. Lesions are most commonly seen in patients with ESRD and hyperparathyroidism, however, diabetes, obesity, female sex, liver disorders, hyperphosphatemia, hypercoagulable states, vitamin K deficiency, autoimmune diseases, metastatic malignancies, ultraviolet rays' exposure, prolonged warfarin therapy and steroids are also reported as risk factors [1-3]. We present a rare case of warfarin-induced calciphylaxis in a patient with no other risk factors.

2. CASE PRESENTATION

A 48-year old Indian male (BMI 23 kg/m2) was presented with a painful ulcer on his right leg. It started as a small swelling six months ago and subsequently developed into a painful ulcer in October 2017. His medications included warfarin 5 mg daily for atrial fibrillation (AF) and amlodipine 5 mg OD for hypertension for the last 26 months. He has a remarkable past history of right middle cerebral artery territory Transient Ischemic Attack (TIA) before 26 months. AF was identified during Holter loop monitoring as a part of TIA aetiological investigations. His AF was paroxysmal and no cause of AF was identified in spite of extensive diagnostic work up. His CHA2DS-VASc score for AF was indicative of prophylactic oral anticoagulant drug and was started on warfarin therapy.

At the time of presentation, his oral temperature was 100.6 F, pulse rate 100 per minute regular in rhythm and right arm blood pressure was 130/80 mm Hg. His cardiorespiratory and neurological examination was unremarkable. Examination of the right lower extremity revealed a tender 5x8 cm necrotic ulcer with serosanguinous discharge, surrounded by purpuric plaques. His hemogram was showing leucocytosis with neutrophilia, erythrocyte sedimentation rate and C-reactive protein were elevated. His renal function tests, liver function tests, metabolic profile, coagulation profile, bone metabolism work up including calcium phosphate product and thyroid functions were within normal limit (Table **1**). Further work up including anti-nuclear antibody, antineutrophilic cytoplasmic antibody, antiphospholipid antibody, IgM anti-CCP, protein C, protein S and antithrombin 3 was in the normal range. X-RAY of the right leg revealed reticular vascular and superficial soft tissue calcifi-

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Table 1. Laboratory values with normal range.

Parameter	Laboratory Value	Normal Range
HAEMOGLOBIN	15.4 Gm%	13.5 – 18 Gm%
TOTAL LEUCOCYTE COUNT	14800/ cmm	4000-10000/ cmm
N/L/B/E/M	80/14/0/2/4	40-70/20-40/0-1/2-10/1-6
ESR	80 mm/Hour	Male < 10 mm/ Hour
C-REACTIVE PROTEIN	25.3 mg/L	< 5.0 mg/ L
BLOOD UREA	25 mg/L	15-39 mg/ L
SERUM CREATININE	0.7 mg/DL	0.7-1.3 mg / DL
SERUM SODIUM	134 mEq/L	136-145 mEq/L
SERUM POTASSIUM	4.0 mEq/L	3.5-5.1 mEq/l
SERUM CHLORIDE	98 mEq/L	98-107 mEq/ L
SERUM BILIRUBIN	0.8 mg/L	0.2-1.0 mg/ L
SERUM ALKALINE PHOSPHATASE	78 u/L	46-116 u/L
SERUM ALT	15 u/L	Male <16 u/L
SERUM ALP	12 u/L	Male <14 u/L
INR (PT)	0.9 IU(13.2 SECONDS)	1.02 lU
SERUM CALCIUM (IONIZED)	5.2 mg/dl	4.6-5.3 mg/dl
SERUM MAGNESIUM	1.8 mg/ dl	1.6-2.3 mg/dl
SERUM PHOSPHATE	4 mg/dl	2.5-4.5 mg/dl
SERUM VITAMIN D3	34 ng/dl	20.1-150ng/ml
SERUM URIC ACID	4.6 mg/dl	3.5-6.2 MG/DL
SERUM TSH	0.8 ulU/dl	0.55-4.78 uIU/ml
SERUM T3	0.8 ng/ml	0.6-1.81 ng/ ml
SERUM T4	6.3 ug/dl	4.5-10.9 ug/dl
SERUM PTH	13 pg/ml	10-69 pg/ ml

cations. Electrocardiogram was showing normal sinus rhythm and a 2-D echocardiogram was unremarkable.

Dermatologist opine provisional diagnosis of panniculitis with secondary infection and skin biopsy after control of local skin infection was suggested. Skin punch biopsy was performed from the margin of the skin ulcer. Histopathology study of the biopsy revealed intravascular calcification involving small subcutaneous vascular channels with micro thrombi of capillaries, changes of panniculitis, necrosis of adipocytes and some of the adipocytes were filled with basophilic granules, suggestive of calciphylaxis. Aetiology of the lesion like end-stage renal disease, hyperparathyroidism, connective tissue diseases or any associated risk factors were unrevealed in spite of extensive diagnostic work up. We speculated warfarin or amlodipine as a cause of calciphylaxis in this case and Naranjo Algorithm (NA) scores for Adverse Drug Reaction (ADR) were calculated for both the drugs. NA for warfarin was 7, while for amlodipine was 1. Hence, warfarin adverse drug reaction was probable (NA- 5 to 8) cause. The drug was discontinued and it was replaced by rivaroxaban. He was discharged with appropriate wound care, analgesics and rivaroxaban. His ulcer healed within four months and there had been no recurrence noted during the one-year follow-up.

3. DISCUSSION

Calciphylaxis is classified in two varieties, one is uremic associated with uraemia and another non-uremic type associated with normal renal functions like obesity, chronic liver disorders and drugs. Calciphylaxis of uremic origin is associated with a high morbidity and mortality in comparison to non-uremic causes. Raised calcium phosphate product is responsible for extensive calcium deposition and calciphylaxis in ESRD, hypercalcemia and hyperphosphatemia [1]. This classical mechanism is not explaining the pathophysiology of non-uremic calciphylaxis.

An imbalance between promoters and inhibitors of calcium metabolism in the vessel wall leads to vascular calcification. Vascular smooth muscle liberates Matrix GL1 Protein (MGP) and it is converted to carboxyl MGP by vitamin K. Carboxyl MGP is a strong inhibitor of vascular calcification

and its relative reduction is associated with calciphylaxis. Bone morphogenic protein (BMP) 2 and BMP 4 are promoters of vascular calcification and are inhibited by carboxyl MGP [1-3]. An individual with certain genetic defects or protein abnormalities other than MGP for vessel wall calcium homeostasis is another mechanism for warfarin-related calciphylaxis.

CONCLUSION

In our case, calciphylaxis was probable ADR of warfarin. This drug being a vitamin K antagonist might lead to a reduction of carboxyl MGP level and this is the speculated mechanism of calciphylaxis due to the drug. This drug is described as a risk factor in some cases, however, in most of those cases, additional risk factors as described earlier were present [2-5]. Only very few cases reported no risk factor other than previous warfarin usage in the literature [5-7]. Calciphylaxis is twice more common in female and it is reported in the fifth decade of life [8]. In contrast to this, our patient was in the 4^{th} decade and of the male gender.

Calciphylaxis is described as the equivalent of cutaneous heart attack and it mimics many dermatological conditions like skin necrosis, venous stasis ulcer, pyoderma gangrenosum, purpura fulminans, necrotizing vasculitis, cholesterol embolism, cellulitis, lupus panniculitis and many more [1]. Close differential diagnosis in our case was warfarin induced skin necrosis, but it manifests early in the course the therapy (within a few weeks), while calciphylaxis develops average after 32 weeks of the drug treatment. Skin biopsy is the gold standard tool for confirmation of the diagnosis. There is no definite treatment for this condition, but local wound care, pain management by opioid analgesics and discontinuation of the offending drug, sodium thiosulfate and hyperbaric oxygen also have seemed to benefit patients in few cases. Sodium thiosulfate is used intravenously in diluted form and is used for local wound care also. It acts by calcium chelating property, inhibition to direct vascular inhibition, and antioxidant vasodilator actions. Uremic calciphylaxis requires haemodialysis with sodium thiosulfate and avoidance of calcium preparations and phosphate binders

Due to the high mortality and morbidity of calciphylaxis, it is imperative for the physicians to have a sound knowledge of this rare condition to avoid late diagnosis and mismanagement of patients. Patients having multiple risk factors of warfarin related calciphylaxis, newer anticoagulant agents are good alternatives.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written and informed consent was obtained from the patient for this study.

STANDARD FOR REPORTING

The CARE guidelines and methodologies were followed in this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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