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Calciphylaxis Masquerading as Warfarin Induced Skin Necrosis

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Abstract Calciphylaxis is rare complication of end stage renal disease on hemodialysis. Calciphylaxis closely mimics warfarin induced skin necrosis in dialysis patients who are being started on coumadin thus posing a diagnostic challenge. Skin biopsy may be required in such cases to confirm the diagnosis.

Keywords: *warfarin skin necrosis, caliphylaxis*

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1. Introduction

Calciphylaxis also termed as calcific uremic arteriolopathy (CUA) is one of the very rare complication of end stage renal disease on dialysis (ESRD) [1], whose incidence has been increasing in the united states as per analysis of united states renal data system. [2] The occurrence of calciphylaxis excalates in the presence of risk factors like exposure to drugs like warfarin, calcium based binders, systemic glucocorticoids. [3,4] Many studies have shown that warfarin poses a major risk in developing CUA. Warfarin induced skin necrosis(WISN), which is a major differential to CUA is a known but relatively rare complication of coumadin, if severe impends a high risk of morbidity and mortality. We present a case of biopsy proven calciphylaxis initially treated as warfarin induced skin necrosis in a patient with ESRD on peritoneal dialysis (PD).

2. Case Report

A 60-year-old man with a history of ESRD on hemodialysis, antithrombin deficiency with history of venous thromboembolism on lifelong warfarin therapy was seen in the urology outpatient office for a reddish skin lesion predominantly distributed over the tip, shaft of the penis which was diagnosed as superficial skin infection and was treated with systemic cephalosporins, he also had supra-therapeutic INR of 7 and hence his warfarin was withheld. After a week he was reassessed by the urologist,as his skin lesions had not improved and now had developed discharge from the tip of the penis which was sent for culture. Patient was given one dose of intramuscular ceftriaxone and oral amoxicillin-clavulinic acid for 7days, as his INR was 1.5, he was restarted on warfarin. When seen after 5 days of treatment in Urology office, his skin lesions appeared gangrenous (Figure 1), with new gangrenous lesions on the back (Figure 2 & Figure3) and infra-umbilical region (Figure 1), drainage culture was positive for Methicillin resistant staphylococcus aureus (MRSA) and Vancomycin resistant enterococcus (VRE) and was hospitalized for the above chief complaint. In hospital, upon admission, patient had a temperature of 34.3, blood pressure of 90/40mmhg, heart rate of 80, respiratory rate of 18 and leukocyte count of 29,300. The remaining of physical examination was normal except of necrotic skin lesions on the back, infra-umbilical and shaft of penis. A diagnosis of Sepsis secondary to MRSA and VRE skin infection was made and patient was started on weight based Daptomycin regimen. The necrotic skin lesion was initially recognized as CISN for which warfarin was discontinued, conservative wound care management was started. To exclude CUA serum calcium and phosphorous was obtained which was within normal limits. As the skin lesions were not getting better, skin biopsy was planned as a confirmatory test. Skin biopsy from posterior lateral lumbar back was positive for chronic active inflammation, dystrophic calcification a suggestive of calcinosis cutis secondary to calciphylaxis. Sodium thiosulphate was initiated as a treatment of calciphylaxis and lesions started to heal as per expectation.

3. Discussion

Calciphylaxis, once known to be a rare entity, has become more common as the number of patients requiring hemodialysis or peritoneal dialysis has become more rampant [8,9]. The theories on pathophysiology of calciphylaxis are many. Calciphylaxis was first identified in 1961 as a systemic hypersensitivity reaction [5], later it was suspected that metabolic abnormalities that are associated with uremia, such as secondary

hyperparathyroidism, hyperphosphatemia, hypercalcemia, and calcium-based phosphate binders, are precipitating factors in CUA [6]. Warfarin contributes to CUA by inhibiting vitamin K–dependent carboxylation of matrix-Gla protein, reducing activity of the protein to inhibit local calcification process [7] which might have contributed for CUA in our patient. However, the exact pathogenesis of CUA is not well known, and specific factors that contribute to this disorder in an individual patient are not well explained. When patient is on dialysis due to ESRD and on warfarin for anti-coagulation the incidence of calciphylaxis increases.

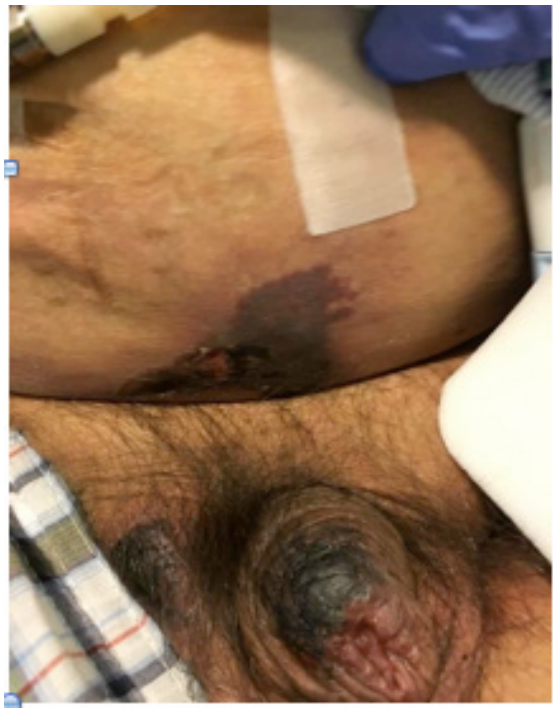

Figure 1. Gangrenous lesion on penis and Below umblicus

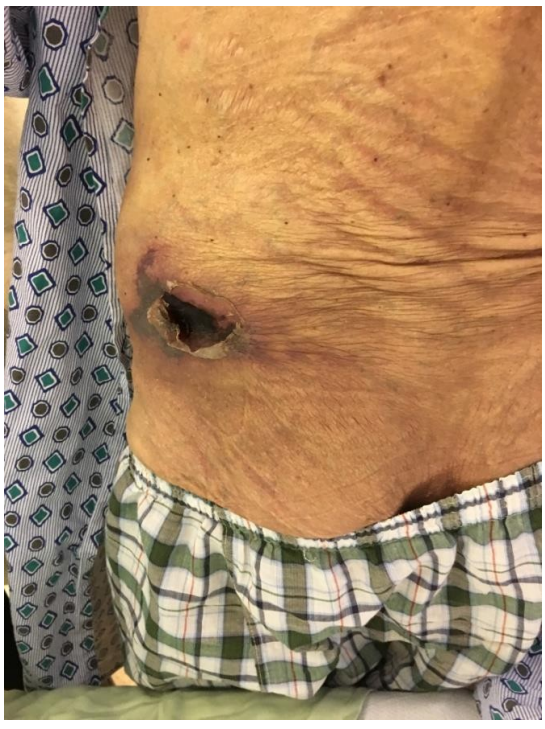

Figure 2. Gangrenous lesion on left Lumbar region

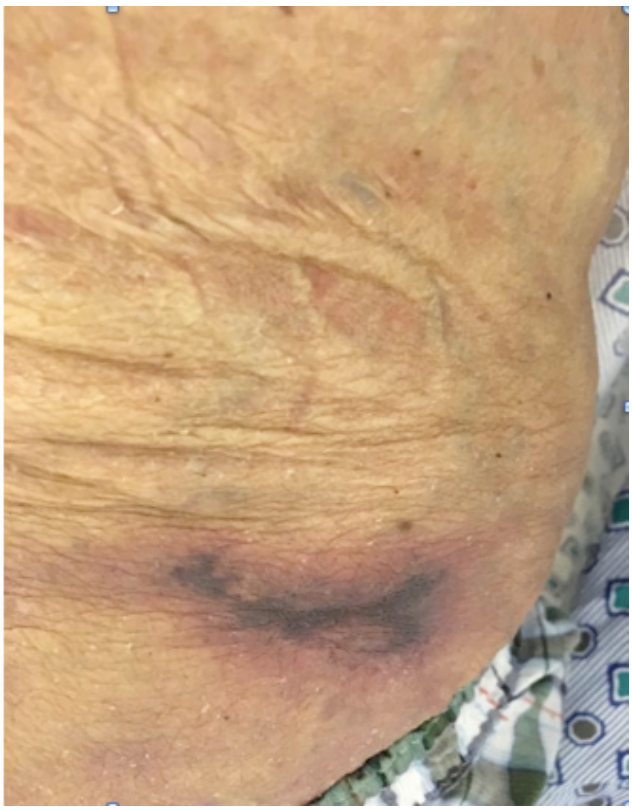

Figure 3. Gangrenous lesion on right lumbar region

Warfarin induced skin necrosis is a potential differential of calciphylaxis which makes the diagnosis even more challenging when patient is on dialysis and warfarin. In some patients, increase in parathyroid hormone (PTH), phosphorous, calcium, and the calcium x phosphorous (Ca x P) product may be seen, although not all patients will present with these abnormalities, especially when patient is on dialysis. In such conditions, skin biopsy plays a vital role is differentiating the former from the latter. Biopsy results of CISN demonstrates fibrin and thrombi in small dermal vessels with no evidence of inflammatory infiltration [10,11], whereas results of CUA show shows arteriolar occlusion and dystrophic calcification.

Sodium thiosulfate has been proposed as a recent and effective treatment option for calciphylaxis as spectacular improvements with pain reduction, reduced inflammation and acceleration of wound healing have been noted within a few days to months of initiationof therapy. Sodium thiosulfate was initially used as a chelating agent for cyanide toxicity, which gained importance in treatment of calciphylaxis in 2004 [12,13]. The proposed mechanism of action is that it would dissolve the insoluble calcium salts embedded in tissue, which makes it easily dialyzable. The more advanced studies have shown added efficacy with combination of Sodium thiosulfate and continuous venovenous hemofiltration (CVVH) [14].

4. Conclusion

Calciphylaxis once known to be a rare entity has gained recognition due to increasing cases of ESRD undergoing dialysis.The occurrence of calciphylaxis increases with risk factors such as concurrent usage of warfarin, secondary

hyperparathyroidism, hyperphosphatemia, hypercalcemia, and calcium-based phosphate binders. As the prognosis of CUA is worse with more than 80% mortality with severe CUA, early diagnosis and initiation of treatment plays a key role. The most common differential diagnosis of CUA is WISN especially, when patient is on warfarin. The prime focus of our case report is to stress the importance of skin biopsy in the differentiating the former from the latter as not all patients would present characteristic lab changes of, increase in parathyroid hormone (PTH), phosphorous, calcium, and the calcium x phosphorous (Ca x P) product. Sodium thiosulfate is a proven and more accepted therapeutic option, while prevention of secondary infection is more life saving.

Conflicts of Interest

None.

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