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RESEARCH ARTICLE

CALCIPHYLAXIS, ANOTHER FACET OF MASTITIS: A CASE REPORT

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Abstract

Introduction: Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare but dreaded condition in patients with chronic renal failure (CRF), whether they are on dialysis or not. Case report: A 67-year-old woman with a 10-year history of chronic renal failure, undergoing hemodialysis, presented with bilateral mastitis characterized by severe lancinating pain and non-healing tissue loss despite medical treatment with antibiotics and anti-inflammatory drugs. Mammography provided limited imaging findings. The diagnosis of calciphylaxis was established after bilateral surgical biopsy.
Discussion: Calcific uremic arteriolopathy, or calciphylaxis, is a rare but life-threatening disease associated with chronic renal failure. Its diagnosis can be challenging. Skin biopsy is considered the gold standard for establishing the diagnosis, but it is not without risks. Recognizing typical skin lesions is important for initiating appropriate management. The management of these patients is multidisciplinary and involves several aspects. In certain cases, the clinical situation may not allow for a cure, and palliative care options will be proposed.
Conclusion: Calcific uremic arteriolopathy is a dreaded condition that primarily occurs in patients with known chronic renal failure, whether they are on dialysis or not. The prognosis is very grim. It relies on a careful examination of the lesions and the exclusion of various differential diagnoses. A multidisciplinary approach is essential to prevent the progression of the lesions and facilitate healing.

Introduction:-

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare but dreaded condition in patients with chronic renal failure (CRF), whether they are on dialysis or not (1). This condition affects patients undergoing hemodialysis, peritoneal dialysis, and kidney transplant recipients. Today, the mechanisms of action and onset of calciphylaxis are better understood. In reality, this condition corresponds to a thrombotic microangiopathy of cutaneous arterioles that does not involve a hypersensitivity reaction. Therefore, the term calcific uremic arteriolopathy is more appropriate (2). AUC is a rare disease, with a prevalence of approximately 5% among dialysis patients (3). The mortality rate is very high, reaching 60-80% at 1 year (4), with the most common cause being superinfection of the cutaneous lesions. The median survival of dialysis patients is shorter than that of non-dialysis patients. The incidence has increased in recent years, which may be explained by better detection (4). The case report we are about to discuss concerns a rare localization of this condition in the breasts of a patient with chronic renal failure undergoing hemodialysis.

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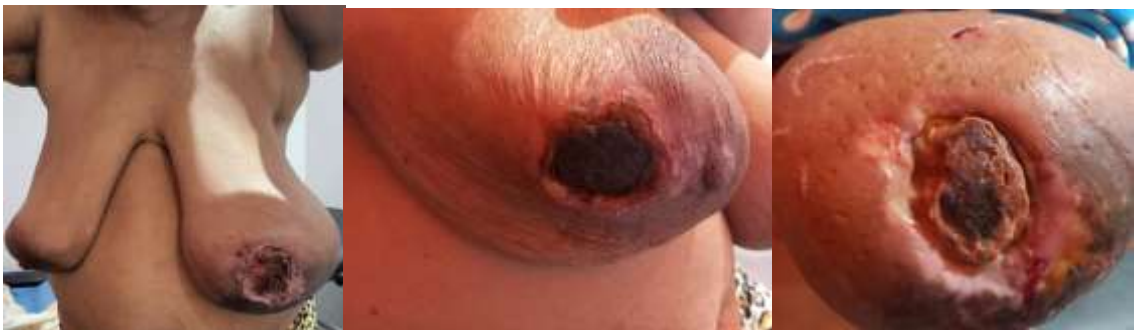
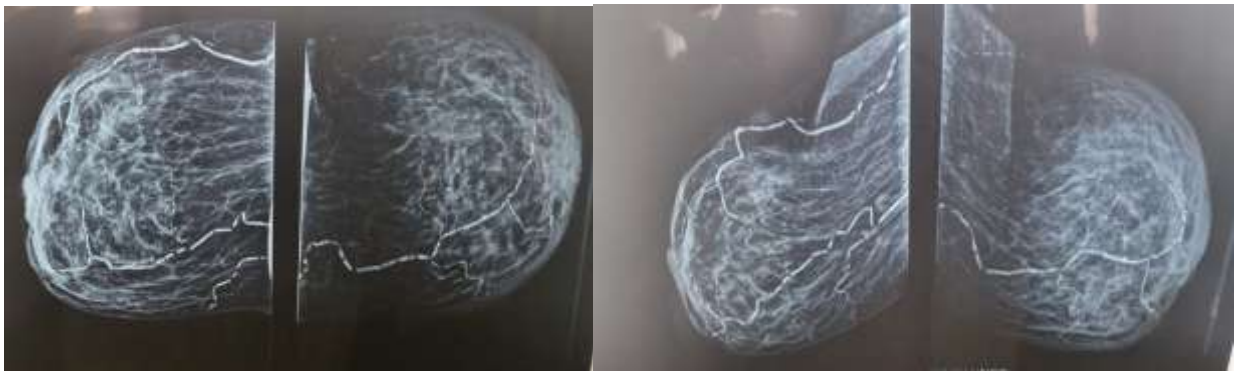
Observation:-

Mrs. K.O., aged 67, has been followed for chronic arterial hypertension and end-stage chronic renal failure for the past 10 years, undergoing hemodialysis. The history of her disease dates back to 6 months prior to her admission, when she experienced bilateral mastodynia characterized by lancinating pain, associated with violaceous skin lesions and tissue loss in the breast area. Upon clinical examination, her BMI was 31 kg/m², and she appeared generally unwell with a performance status of 3. Examination of the breasts revealed enlarged breasts, with the left breast showing increased volume, orange peel skin texture, redness, and tissue loss around the areola. The right breast exhibited extended redness, orange peel skin texture, without palpable nodules, but with necrosis in the peri-areolar region. The axillary lymph nodes were non-palpable.

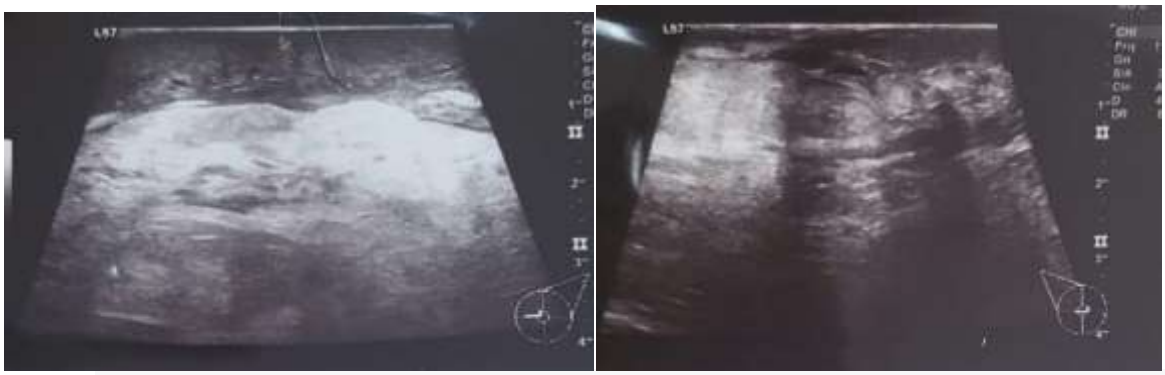
An ultrasound mammography was performed, indicating a significant mastitis predominantly located retro-mammary in the left breast, without focal lesions or obvious mass syndrome. The patient was treated with anti-inflammatory drugs and antibiotics for one month, but there was no significant improvement. A follow-up ultrasound mammography showed bilateral mastitis without parenchymal lesions. It was recommended to perform a bilateral surgical biopsy, and the histological result revealed fibro-inflammatory remodeling with hyper-vascularization, small foci of ischemic necrosis, and vascular calcifications. This appearance is consistent with calciphylaxis related to chronic dialysis without signs of malignancy.



Figures 1:- Clinical aspect of skin lesions around the areolas with tissue loss.



Figures2:- Follow-up mammography: Bilateral peri-areolar increased density, predominantly on the right, with skin thickening in that area. No microcalcification clusters observed. Clear axillary extensions.



Figures 3:- Follow-up breast ultrasound: Significant skin thickening with diffuse edematous infiltration of the fatty tissue in the retro- and peri-areolar regions, as well as in the right upper inner quadrant and left upper inner quadrant. No visible solid nodules. Benign lymph nodes in the axillary regions.

Discussion:-

Calciphylaxis is a rare disease with high mortality, caused by calcification and occlusion of the microvessels in the dermis and hypodermis (5). The close link between calciphylaxis and chronic kidney disease (CKD) treated with dialysis was established in the 1990s (6). The terms "uremic calciphylaxis" (UC) and "calcific uremic arteriolopathy" were then proposed to distinguish the form associated with CKD, which is the most common, from the form without renal insufficiency, which is exceptional (7). Our understanding of the pathophysiology of this disease has evolved. It initially revealed the importance of mineral and bone abnormalities in CKD (8), followed by the major role of vitamin K antagonists (VKA) in the formation of arteriolar microcalcifications in UC (8). This review focuses on uremic calciphylaxis. Although it is the most frequent and best-known form, its prognosis remains grim, with a one-year mortality ranging from 40 to 80% (9), compared to 25 to 45% for non-uremic calciphylaxis (10). Understanding the clinical presentations and diagnostic tools for UC should enable early diagnosis and prompt management. Its association with CKD, mineral and bone abnormalities, and VKAs calls for preventive measures and guides curative treatments. These treatments are complex and multimodal, requiring regular assessment of the proportionality of care (10).

UC manifests with specific skin lesions: violaceous plaques with a necrotic center, surrounded by an extremely painful pink border, and indurated subcutaneous nodules (3). Pain sometimes precedes the appearance of skin lesions. This excruciating pain is of ischemic and neurogenic origin. The lesions typically occur in adipose areas such as the abdominal fat, flanks, buttocks, and inner thighs. In women, the breasts can also be affected. Rarely, UC can involve internal organs (digestive tract, lungs, heart, or eyes) and distal extremities (lower limbs, fingers, or penis) (3).

Several risk factors have been identified. Women are more commonly affected than men. Caucasian race, duration of CKD, time on dialysis, diabetes, liver disease, obesity (BMI > 30 kg/m2), and autoimmune diseases (such as lupus, antiphospholipid antibodies, Horton's disease, rheumatoid arthritis, etc.) are recognized risk factors (4). Disorders of phosphocalcium metabolism are also implicated: secondary hyperparathyroidism, increased phosphocalcium product, hyperphosphatemia, and vitamin D deficiency. Several medications are also implicated in the development of UC:

Calcium supplements, calcium phosphate chelators, active vitamin D, corticosteroids, and vitamin K antagonists (11). Intravenous iron supplementation also appears to be correlated with the development of UC lesions (12). Subcutaneous insulin injections create microtrauma that can precipitate lesion development. Vascular calcification results from dysregulation of phosphocalcium metabolism. Two calcification inhibitors play a key role in this mechanism: fetuin-A (a2-Heremens-Schmid glycoprotein) and matrix Gla protein (MGP) (3). Fetuin-A, produced by the liver, inhibits hydroxyapatite formation by binding to serum calcium and phosphate. This protein is decreased in cases of inflammation and CKD. MGP is a vitamin K-dependent protein. It is therefore inhibited by vitamin K antagonist treatments, such as acenocoumarol or warfarin, explaining the association between vitamin K antagonists and UC. MGP is mainly present in smooth muscle cells of vascular walls and chondrocytes. The uremic environment, particularly associated microinflammation and the presence of free radicals, also play a central role through the activation of nuclear factor kappa beta (NF-κB) and overexpression of endothelin-1.

Moreover, the transdifferentiation of vascular smooth muscle cells into osteoblast-like cells is a crucial element in vascular calcification. Additionally, the state of hypercoagulability is also significant in the development of UC lesions (13). Activation of inflammatory cytokines IL-1, IL-6, and TNF-α leads to decreased expression of protein C and S receptors, decreased expression of thrombomodulin, and release of tissue factor (3). All of these factors contribute to endothelial dysfunction, promoting thrombotic occlusion. The diagnosis of UC is often challenging. There is no specific biochemical analysis or radiological examination that can provide a precise diagnosis. Various imaging modalities have been studied, but none can definitively diagnose UC. The gold standard for confirming the diagnosis remains skin biopsy (3). However, this procedure is debated. It has the potential to cause additional trauma, creating new areas of necrosis and ulceration that worsen existing cutaneous lesions. For this reason, performing a biopsy is reserved for patients with uncertain diagnoses (14).

The histology of an AUC wound shows calcification of the arteriolar media, intimal proliferation, calcification of perivascular soft tissues, and epidermal necrosis (3). The dermis separates from the epidermis. Additionally, analysis of the subcutaneous tissue reveals panniculitis. Specific stains such as von Kossa and Alizarin Red can identify microcalcifications. The management of AUC should be multidisciplinary. There are no approved treatments for this condition. However, principles can be derived from the literature (4):

• Debridement of the cutaneous lesions combined with appropriate antibiotic therapy
• No consensus on the type of surgical resection. Some recommend limited procedures due to difficulties in wound healing, while others prefer extensive excision of the lesions.
• Tissue oxygenation, as ischemia appears to play a significant role.
• Pain management
• Slowing down the process of vascular calcification by maintaining strict control of the phosphocalcium metabolism (diet, medical treatments: sodium thiosulfate, etc.)

Pain control is essential. The assistance of a specialized team is often required due to the excruciating pain caused by the cutaneous lesions. Additionally, meticulous wound care with daily dressing changes is necessary to minimize the risk of infection. However, caution should be exercised during wound debridement to avoid causing additional trauma (15). Hyperbaric oxygen therapy sessions should be considered as part of the management. Correcting the phosphocalcium balance is paramount (15). Calcium supplementation and calcium phosphate binders should be discontinued. Non-calcium phosphate binders are recommended. There is no indication for therapeutic anticoagulation, except in patients previously known to have a hypercoagulable state. Vitamin K antagonists are contraindicated, but the efficacy of routine vitamin K supplementation is not established. Daily hemodialysis treatment with a low-calcium bath (1.25 mmol/L) is also advised. Pharmacological management involves intravenous administration of sodium thiosulfate (low oral bioavailability) (13). Its mechanism of action is not fully understood. Its vasodilatory and antioxidant properties increase the solubility of calcium and its precipitation into a dialyzable salt. This treatment is administered three times per week at an empirical dose of 25 grams during the last hour of hemodialysis. The same dosage is recommended for patients on peritoneal dialysis. There is no defined indication for changing to a different modality such as hemodialysis. For non-dialysis patients, a dose adjusted to renal function will be prescribed. Side effects include nausea, rare vomiting, and headaches. Metabolic acidosis can also occur and be severe. Treatment should continue for up to two months after complete healing of the cutaneous lesions. It is worth noting that pain relief may occur quickly, within a few days of treatment, but complete healing takes much longer (from weeks to several months). Finally, in some cases, the choice of palliative treatment may be justified, for example, in the presence of unbearable pain or significant comorbidities (15). An open discussion with the patient should take place to decide on the most appropriate management approach together.

Conclusion:-

L'artériolopathieurémiquecalcifianteest indeed a redoutable condition that mainly affects patients with known chronic kidney disease, whether they are on dialysis or not. The prognosis is very poor. It relies on a thorough examination of the lesions and the exclusion of several differential diagnoses. Correcting the phosphocalcium balance and discontinuing implicated treatments are essential. Furthermore, a multidisciplinary approach is indispensable to prevent the progression of the lesions and facilitate their healing.

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