Understanding calcinosis and calciphylaxis

KEY WORDS
- Calcinosis cutis
- Calciphylaxis
- Warfarin-induced skin necrosis

Calcinosis cutis is a rare cause of non-healing leg ulceration. There are many factors that can delay the healing of venous leg ulceration and the deposition of calcium in the skin known as calcinosis cutis is one of these factors. There are five distinct forms: dystrophic calcification, metastatic calcification, idiopathic calcification, iatrogenic calcification and calciphylaxis. Warfarin skin necrosis has common clinical features with calciphylaxis and is therefore included in this article, which describes the types of calcinosis cutis, their clinical presentations and limited treatment options. The aim is to highlight these unusual causes and to assist healthcare professionals when faced with a non-healing ulcer.

TRUDIE YOUNG
Director of Education and Training, Welsh Wound Innovation Centre, Ynysmaerdy, Rhondda Cynon Taff, Wales

Leg ulceration can be defined as a defect in the dermis located on the leg (Franks et al, 2016). Leg ulceration is a significant clinical problem with the majority attributing venous hypertension as the underlying disease process with venous leg ulceration affecting 1% of the population in the western world (Posnett et al, 2009). However, there is a multitude of causative factors of leg ulcers, with the term leg ulcer purely signifying the clinical manifestation and not the underlying aetiology.

In certain situations, despite confidence in the diagnosis, the leg ulcer fails to respond to appropriate treatment and make the expected progression. Under these circumstances, the healthcare professional should revisit the assessment process to establish if there is an alternative diagnosis that may have been overlooked (Franks et al, 2016). Calcinosis and calciphylaxis are rare causes of delayed healing in individuals with leg ulceration.

CALCIUM

Most calcium in the human body is in a relatively insoluble form. It is the primary mineral in the bony skeleton and is also found in teeth. The remainder is found in a soluble form in the intracellular and extracellular space, e.g. cytoplasm. Calcium is involved in skeletal muscle and myocardial contraction as well as neurotransmission and the blood coagulation pathway. At a cellular level, it is implicated in cell-to-cell communication (Walshe and Fairley, 1995). In the skin, it is specifically concerned with keratinocyte proliferation, differentiation and adhesion (Smith and Yamada, 2002).

The level of serum calcium is closely controlled by the parathyroid hormone. Regardless of this regulation, it is possible for calcium salts and minerals to be deposited in cutaneous and subcutaneous tissue (Walshe and Fairley, 1995; Kupitz et al, 2007).

Calcification is an acquired disorder in which there is deposition of insoluble calcium in cutaneous tissue. Large amorphic deposits might also be found in subcutaneous tissue (calcinosis cutis), and in mural calcification calcium can be found within the walls of the arteries (Pugashetti et al, 2011).

There are four types of calcinosis cutis: dystrophic calcification, metastatic calcification, idiopathic and iatrogenic calcification with calciphylaxis now added as the fifth variant (Reiter et al, 2011a) *(Table 1)*.

DYSTROPHIC CALCIFICATION

Dystrophic calcification (DC) is the most common type of calcinosis cutis, although it can also occur in muscles and tendons (Smith and Yamada, 2002;

Table 1. Types of calcification

Type of calcinosis cutis	Trigger	Diagnostic assessment	Levels of serum calcium/phosphate	Associated conditions	Internal organs affected	Physiological presentation	Common sites	Clinical presentation	Specific treatment
Dystrophic	Tissue trauma and structural damage to the skin	X-ray, analysis of calcium deposits once removed from the wound bed	Normal	CREST Syndrome, Systemic Lupus Erythematosus, Panniculitis, Ehlers-Danlos syndrome	No	Multiple and local deposits of calcium	Leg ulcers, injection sites, non-viable tissue, fingers, elbows, forearms	Presence of hard calcium grainy deposits in the wound bed, chalky exudate	Removal of calcium deposits in the wound bed
Metastatic	Hypercalcaemia and/or hyperphosphatemia,	Haematological investigation, x-ray	Abnormal	Chronic kidney disease	Kidney, lungs	Multiple and local deposits of calcium	Subcutaneous and deep tissue, e.g. gastric mucosa, arteries and veins	Depending on the area affected	Stabilisation of calcium and phosphate levels, alteration in method of renal dialysis
Idiopathic	Unknown	X-ray	Normal	Familial forms present and seen in infants	No	Calcification of subcutaneous tissue	Localised, scrotum, around major joints, head, extremities	Nodules under the surface of the skin	No specific recommendations
Iatrogenic	Intravenous infusion of calcium chloride and/or calcium gluconate	Clinical presentation	Normal	None	No	Elevated tissue concentration of calcium at the extravasation site	Local to intravenous infusion site	Calcium deposits at the site of the extravasation injury	Resite the intravenous infusion
Calciphylaxis	Renal transplantation, end stage renal disease	Tissue biopsy, X-ray	Abnormal or normal in the presence of hypercoagulability states	Obesity, female gender, diabetes mellitus, secondary hyper-parathyroidism and Warfarin medication	Potential	Calcium deposits in skin, small and medium sized blood vessels producing clot formation within the vessels	Areas with an increase in subcutaneous fat, e.g. abdomen, buttocks, thighs, lower legs and feet with the latter two sites producing less severe clinical outcomes	Mottled skin (retiform purpura), purple blood blisters, nodules, skin necrosis, ulcers with a violaceous edge	Parathyroidectomy if hyperparathyroid disease, wound debridement and removal of calcium deposits, Treatment systemically and locally if infection/sepsis occurs. In renal failure alter method of dialysis to one with a lower calcium concentration
Warfarin induced skin necrosis	Commenced warfarin as an anticoagulant therapy within the preceding 24–48 hours	Skin biopsy	Normal	Female, obesity	No	Microthrombi in dermal and subcutaneous tissue, venules and deep veins, endothelial cell damage, red blood cell extravasation	Areas with an increase in subcutaneous fat, e.g. abdomen, buttocks, legs, thighs, mammary tissue	Paraesthesia, oedema, mild rash, skin necrosis	Alternate form of anticoagulation, wound debridement

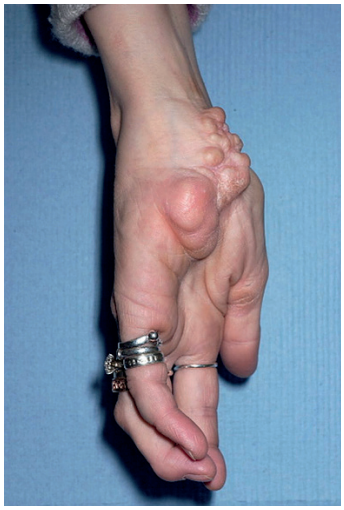

Figure 1. Hand of a patient with idiopathic calcinosis

Walshe and Fairley, 2005). Importantly, in DC, the serum calcium and phosphate levels are within the normal limits and the internal organs are unaffected (Enoch et al, 2005). DC occurs in cases of local tissue trauma or abnormality, structural damage to collagen, elastin, proteoglycans and subcutaneous fat resulting in multiple and local depositions of calcium (Enoch et al, 2005; Kupitz et al, 2007; Reiter et al, 2011a). The structural damage may be due to skin trauma including leg ulceration, injection sites, pressure damage and self-inflicted injuries (Pugashetti et al, 2011). DC can be present in locally dead or dying tissue such as slough and necrosis in the wound bed (Kumar et al, 2015). Sometimes, the DC remains unidentified until it is discovered during an incidental radiological investigation (Enoch et al, 2005).

DC occurs in connective tissue diseases, e.g. systemic scleroderma (which include CREST syndrome and progressive systemic sclerosis) and systemic lupus erythematosus (Kupitz et al, 2007; Al-Najjar and Jackson, 2011), and in cases of panniculitis, an inflammatory process primarily affecting the subcutaneous fat layer (Walshe and Fairley, 2005). Certain groups of inherited disorders of collagen metabolism can result in DC, e.g. Ehlers-Danlos syndrome (Walshe and Fairley, 2005).

In due course, the areas of the skin with underlying calcinosis may ulcerate and exude a chalky material (Walshe and Fairley, 2005). Although visible to the naked eye the calcium deposits may be minuscule, white and grainy in appearance and can be overlooked as an alternative tissue type within the wound bed. The calcium deposits are hard and firmly adhered to the wound bed. The calcium deposits break through into the wound bed and elicit an inflammatory response and as such delay the healing process (Enoch et al, 2005, Al-Najjar and Jackson, 2011).

In calcinosis universalis, there are large and widespread calcium deposits in the subcutaneous tissue in the form of long bands of symmetrical subcutaneous calcification that extend along deep fascial planes. This produces an additional layer of hard calcium that interferes with the body's functions and can involve tendons and ligaments. Due to the severity and restrictiveness of this condition, it is associated with a poor prognosis (Walshe and Fairley, 1995).

METASTATIC CALCIFICATION

Metastatic calcification (MC) is a systematic disorder producing the precipitation of calcium salts in normal cutaneous, subcutaneous and deep tissue (Smith and Yamada, 2002; Enoch et al, 2005), commonly interstitial tissues of the gastric mucosa, kidneys, lungs, systemic arteries and pulmonary veins (Kumar et al, 2015). It usually results from hypercalcaemia secondary to abnormal calcium metabolism (Kumar et al, 2015). There are four main causes of hypercalcaemia:

- Increased secretion of parathyroid hormone caused by hyperparathyroidism (benign or malignant tumours)
- Reabsorption of the bone tissue caused by primary or secondary tumours of the bone or bone marrow, Paget's Disease or immobility
- Vitamin D-related disorders
- Renal failure (Kumar et al, 2015).

Therefore, as opposed to DC, MC is due to abnormal calcium and phosphate metabolism leading to hypercalcaemia and hyperphosphatemia (Enoch et al, 2005; Reiter et al, 2011a). Consequently, MC commonly occurs in patients with renal failure due to a decreased clearance of phosphate and impaired production of vitamin D and the subsequent reduction in the absorption of calcium from the intestine (Smith and Yamada, 2002; Beitz, 2004; Pugashetti et al, 2011).

Pugashetti et al (2011) reported a case where an individual presented with the features of both DC and MC, which is a rare phenomenon. In this case the individual presented with features of MC, secondary hyperparathyroidism and hypercalcaemia. However, the calcification appeared in areas of skin damage that is associated with DC. The authors postulate that the categories of calcinosis cutis may not be as discreet as was first thought and they may overlap in certain individuals.

IDIOPATHIC CALCIFICATION

Unlike DC and MC, idiopathic calcification (IC) occurs without any abnormal calcium or phosphate levels or tissue trauma/abnormalities (Walshe and Fairley, 1995). It has been reported to affect subcutaneous tissue such as the scrotum and is often seen in infants and in familial forms (Enoch et al, 2005) *(Figure 1)*.

REFERENCES

Al-Najjar M, Jackson MJ (2011) Non-healing leg ulcers in a patient with dystrophic calcification and crest syndrome: A challenging clinical case. *International Wound Journal* 8(5): 537–41

Beitz M J (2004) Calciphylaxis: An uncommon but potentially deadly form of skin necrosis. *American Journal of Nursing* 104(7): 36–7

Breakey W, Hall C, Vann Jones S et al (2014) Warfarin-induced skin necrosis progressing to calciphylaxis. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 67(10): e244–6

Enoch S, Kupitz S, Miller DR, Harding KG (2005) Dystrophic calcification as a cause for non healing leg ulcers. *International Wound Journal* 2(2): 142–47

Franks P, Barker J, Collier M et al (2016) Management of patients with venous leg ulcer: Challenges and current best practice. *J Wound Care* 25(6): Suppl 1–67

Kumar V, Abbas A, Aster J (eds) (2015) *Robbins and Cotran Pathological basis of disease.* Elsevier, Philadelphia

Kupitz S, Enoch S, Harding KG (2007) Chronic ulcers, calcification and calcified fibrous tumours: Phenotypic manifestations of a congenital disorder of heterotopic ossification. *International Wound Journal* 4(3): 273–80

Latus J, Kimmel M, Ott G et al (2011). Early stages of calciphylaxis: Are skin biopsies the answer. *Case Rep Dermatol* 3(3): 201–5

Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM (2009) Warfarin-induced skin necrosis. *J Am Acad Dermatol* 61(2): 325–32

Park JE, Byeon S, Kim HK et al (2016) Warfarin skin necrosis mimicking calciphylaxis in a patient with secondary hyperparathyroidism undergoing peritoneal dialysis. *Kidney Res Clin Pract* 35(1): 55–8

Posnett J, Gottrup F, Lundgren H, Saal G (2009) The resource impact of wounds on health-care providers in Europe. *J Wound Care* 18(4): 154–61

Pugashetti R, Shinkai K, Ruben BS et al (2011) Calcium may preferentially deposit in area of elastic tissue damage. *J Am Acad Dermatol* 64(2): 296–301

Reiter N, El-Shabrawi L, Leinweber B et al (2011a) Calcinosis cutis. Part i. Diagnostic pathway. *J Am Acad Dermatol* 65(1): 1–12

Reiter N, El-Shabrawi L, Leinweber B et al (2011b) Calcinosis cutis: Part ii. Treatment options. *J Am Acad Dermatol* 65(1): 15–22

Sajjan VV, Lunge SB, Swamy MB, Pandit AM (2015) Livedo reticularis: A review of the literature. *Indian Dermatology Online Journal* 6(5): 315–21

Sato T, Ichioka S (2012) How should we manage multiple skin ulcers associated with calciphylaxis? *J Dermatol* 39(11): 966–8

Smith RG, Yamada W (2002) Venous stasis ulcer complicated by calcinosis cutis. *Wounds* 14: 122–9

Sulková SD, Válek M (2010) Skin wounds associated with calciphylaxis in end-stage renal disease patients on dialysis. *Nutrition* 26(9): 910–14

Walshe JS, Fairley JA (1995) Calcifying disorders of the skin. *J Am Acad Dermatol* 33(5:1) 693–706

IATROGENIC CALCIFICATION

Iatrogenic calcification (IGC) is a recognised complication of extravasation of intravenous calcium chloride and calcium gluconate, resulting in a locally elevated level of concentration of calcium in the tissue. It presents with painful calcified nodules at the extravasation site which resolve in time following discontinuation of the therapy at the damaged area (Enoch et al, 2005).

CALCIPHYLAXIS

Calciphylaxis was first described in 1898 and still remains a poorly understood condition (Breakey et al, 2014). Calciphylaxis was previously considered as a variant of MC, however, now it is recognised as the fifth variant of calcinosis cutis (Reiter et al, 2011a).

Calciphylaxis has been reported in individuals with normal parathyroid and renal function (Pugashetti et al, 2011; Latus et al 2011). Nevertheless, is it often a complication of renal transplantation and end-stage renal disease (Latus et al, 2011; Breakey et al, 2014; Park et al, 2016). Approximately 1–5% of dialysis patients will develop calciphylaxis (Sulková and Válek, 2010). Risk factors for calciphylaxis include obesity, female gender, diabetes mellitus, secondary hyperparathyroidism and Warfarin medication (Latus et al, 2011; Sato and Ichioka, 2012).

It is characterised by progressive vascular calcification and/or necrosis of the skin (Pugashetti et al, 2011). The small and medium-sized blood vessels of the dermis and subcutaneous fat become calcified causing tissue infarction and ischaemia. In addition, there can be extravascular calcified deposits (Reiter et al, 2011a; Breakey et al, 2014).

The clinical presentation can start with purple-coloured mottling of the skin with blood-filled blisters. It develops into necrotic/violaceous plaques and as thus has similarities to the edges of ulcers caused by pyoderma gangrenosum (Walshe and Fairley, 1995). Nodules can also be present along with mottled skin resembling livedo reticularis. Livedo reticularis is a cutaneous physical sign characterised by transient or persistent blotchy reddish-blue to purple, net-like cyanotic pattern on the skin (Sajjan et al, 2015). In calciphylaxis, the plaques and nodules are often found on the lower limbs and can progress to become multiple non-healing ulcers that are accompanied by tenderness, ischaemic pain and infection (Sulková and Válek, 2010; Reiter et al, 2011a).

Additional differential diagnoses include vasculitis, peripheral arterial disease, venous leg ulceration, necrotising fasciitis and warfarin necrosis (Sulkocá and Válek, 2010).

There are no specific laboratory tests to diagnose calciphylaxis, however, a biopsy will identify calcium deposits within the intima of the arterioles (Sato and Ichinoka, 2012; Breakey et al, 2014).

A high proportion of individuals with calciphylaxis will die within 12 months of diagnosis due to the inability to reverse the vascular disease, with sepsis as the principal cause of death (Sato and Ichioka, 2010). Lesions on the trunk and proximal areas have a worse prognosis than lesions sited elsewhere on the body (Sulková and Válek, 2010).

WARFARIN-INDUCED SKIN NECROSIS

Warfarin-induced skin necrosis (WISN) and calciphylaxis have common clinical features, with Warfarin treatment being a representative risk factor for calciphylaxis (Park et al, 2016). It is known that WISN is a result of the pharmacological effects of warfarin despite a lack of detailed understanding of the exact mechanisms of damage. The clinical presentation is an acute onset within 24 hours (Nazarian et al, 2009). The early clinical picture may be of paresthesia and oedema of the affected area along with a mild skin rash that can then progress to resemble the clinical presentation of calciphylaxis on the limbs and trunk (Breakey et al, 2014; Park, 2015). It often involves areas with increased subcutaneous fat such as the abdomen, buttocks, thighs, legs and mammary tissue in females (Nazarian et al, 2009). The final clinical outcome may be full-thickness skin necrosis with deep subcutaneous ulceration (Nazarian et al, 2009). Calciphylaxis and WISN can be differentiated on histological findings necessitating a biopsy for confirmation of the correct diagnosis (Breakey et al, 2014). The histopathological characteristics include diffuse microthrombi within the dermal and subcutaneous capillaries, venules and deep veins, endothelial cell damage and red blood cell extravasation. Vascular inflammation is not present, therefore, distinguishing the problem from primary vasculitis (Nazarian et al, 2009).

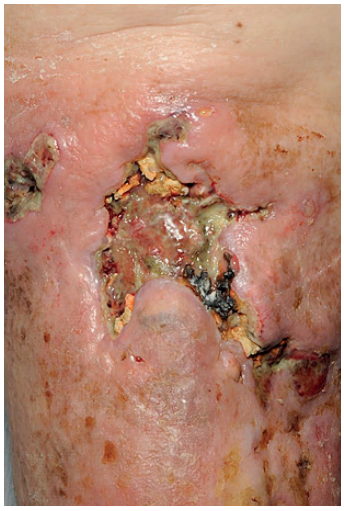

Figure 2. Calcium deposits embedded in the wound bed

TREATMENTS FOR CALCINOSIS CUTIS, CALCIPHYLAXIS AND WISN

There is a notable lack of randomised controlled trials in calcinosis cutis with treatment being reported on a individual or small case series basis (Reiter et al, 2011b).

Systemically, the medical management for the different types of skin manifestations discussed in this article will differ, i.e. WISN requires alternative anticoagulation therapy and in MC control of calcium and phosphate metabolism will be necessary (Park et al, 2016). Surgical intervention may be required in the form of a parathyroidectomy for individuals with hyperparathyroidism (Sato and Ichioka, 2012). In cases of calcinosis in patients with chronic kidney disease, the frequency and type of haemodialysis may be revised (Breakey et al, 2014).

There is no accepted standard wound care treatment for the problem of calcinosis cutis, calciphylaxis or WISN.

The mainstay of localised treatment is the removal of the calcium deposits from the wound bed. This is not always easy to achieve, with deposits being firmly embedded in the wound. Severe pain often accompanies the attempts to remove the calcium deposits, and the use of a topical anaesthetic may help to relieve the pain. Anecdotally, hyperbaric oxygen has been used in some cases to aid with demarcation and debridement of necrotic tissue, although there is no robust evidence supporting its use in these patients. Enoch et al (2005) report the treatment of three patients with DC, which in certain cases had progressed to osteomyelitis. However, even after removal of the calcified deposits they subsequently reappeared within the wound bed and for one individual recurrence occurred following surgical excision and grafting. Extensive surgery (above knee amputation) was reported in an individual with CREST syndrome and venous leg ulceration due to extensive subcutaneous calcification (Al-Najjar and Jackson, 2011).

Treatment of WISN using surgical debridement along with negative pressure wound therapy and/or split skin grafts have been reported in the literature (Breakey et al, 2014).

Figure 2 reveals the presence of calcium deposits in the wound bed of an individual with leg ulceration. The calcified deposits are firm to the touch and have worked their way up from the subcutaneous tissue into the wound bed. Their presentation is not uniform across the wound bed and without palpation, they could visually be confused with dry slough. The calcium deposits are firmly adhered and difficult to remove. As highlighted in the literature, wounds containing these calcium deposits are very difficult to manage. The principles of wound bed preparation require the wound to be readied for healing, which requires debridement of foreign objects from the wound bed. However, due to the firm adherence of the calcium deposits, they do not respond to conventional methods, e.g. autolysis and mechanical debridement. Sharp or surgical debridement is necessary, with the latter being a more pain-free process. Anecdotally, pain can be present if these hard areas are compacted under compression bandages.

The psychological support of the patient with non-healing wounds is paramount as even following successful removal of the calcium deposits from the wound bed they can recur and reinstate the cycle of pain, despondency and non-healing.

CONCLUSION

Leg ulceration can be complicated by the rare presence of calcinosis cutis which can result in delayed healing, amputation and increased mortality.

Calcinosis cutis is the umbrella term for five distinct types of calcification. The main distinctions are the presence or not of abnormal serum calcium and phosphate levels, localised extravasation injury and drug-induced calcification. WISN and calciphylaxis have common clinical features and initially may be difficult to separate by clinical presentation. Histological examination of the tissue is helpful in establishing the aetiology. Regardless of the specific underlying pathology, calcification is common to all variants of calcinosis cutis, with calcium deposits found within the wound bed, surrounding tissues and/or blood vessels. It can result in skin ulceration and necrosis, the presence of the calcium deposits in the wound bed induce a foreign-body type of inflammatory reaction that delays the healing process.

There is no recognised local treatment for ulcers containing calcified deposits, however, extraction appears to be a therapeutic option. Systemic treatments depend on the underlying aetiology and may help to arrest the disease process. WUK