Calcinosis Cutis: Critical Review

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SUMMARY The most widely accepted classification of calcinosis cutis is reviewed and several aspects of it are examined. The main point of our criticism is that entities from different groups overlap. Also, the classification mixes etiopathogenic criteria with morphological or semiologic ones. Moreover, the role of the dermatopathologist is limited many times, since only generic information under the diagnosis "calcinosis cutis" is given to the clinician. Taking these into account, we introduce a possible morphological classification of calcinosis cutis, based on the pattern of the cutaneous deposits.

KEY WORDS: calcinosis cutis, metastatic calcinosis, dystrophic calcinosis, calcinosis classification

INTRODUCTION

The most widely accepted classification of calcinosis cutis is based on pathogenic concepts. It does not offer a wide scope to the dermatopathologist to help the clinician; on many occasions, the former can just confirm that the deposit is consistent with calcium. This contrasts with some classifications of other cutaneous deposits, which sometimes include some morphological aspects.

In this report, several weak aspects of this classification are depicted and a possible alternative one is presented, with special reference to the morphological patterns.

Current classification of calcinosis

Traditionally, three types of calcinosis cutis have been distinguished: metastatic, dystrophic, and idiopathic. Some add a fourth type called iatrogenic (1,2).

Metastatic calcinosis is secondary to hypercalcemia (3) or hyperphosphatemia (4). Therefore, calcium serum levels can be increased or decreased.

Dystrophic calcinosis usually occurs in the dermis, which has previously been damaged. In the physiopathology of the disease, damage to the elastic fibers has been proposed (3). The deposit can be localized, for example, in cutaneous tumors (Fig. 1), cysts, local traumas (Fig. 2) (5-8), burns (9), or frostbite (10). Occasionally, percutaneous penetration has been suggested as the pathogenic mechanism (11).

On the contrary, it can be widespread in conditions such as dermatomyositis (12-16), scleroderma (6,17), lupus erythematosus (18-21), pseudoxanthoma elasticum (22-25), or in Ehlers-Danlos syndrome (26), just to mention some examples. Herpes infection is a rare cause of this widespread type of calcinosis (27). In some publications, when dystrophic calcification is widespread, it is catalogued as "calcinosis universalis" (1), a term that some prefer to use only for widespread idiopathic calcinosis (28).

The term **idiopathic calcinosis** is used for cases in which there is no identifiable underlying cause, or the

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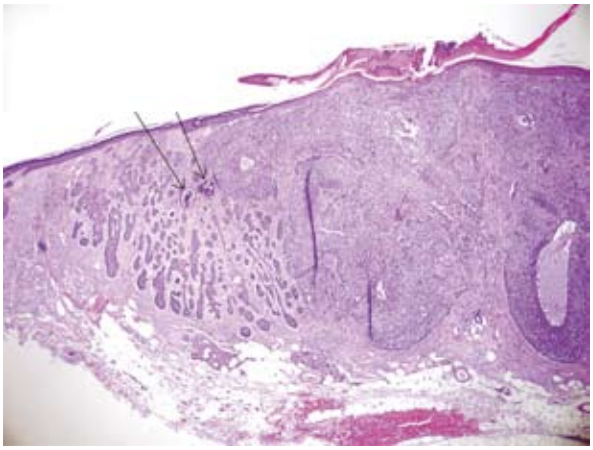

Figure 1. Calcium deposits in a case of trichoblastic (basal cell) carcinoma with peripheral trichoblastoma (HE; x4).

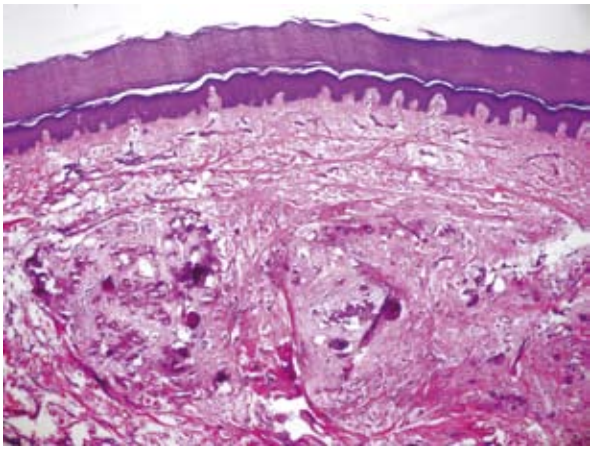

Figure 2. Dystrophic calcification on the knee of a 57-year-old woman, due to local traumatism (HE; x10).

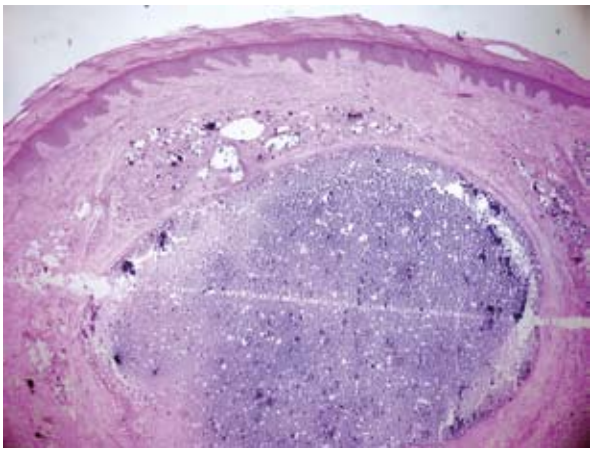

Figure 3. Subepidermal calcified nodule in the left shoulder of a 52-year-old woman (HE; x4).

cause is obscure. It can be localized, as in familial tumoral calcinosis (29), subepidermal calcified nodule (Fig. 3) (30-33), dermal calcinosis and idiopathic calcinosis of the scrotum (Fig. 4) (6,34,35). There is also a generalized form that is known as calcinosis universalis.

The term **iatrogenic calcinosis** is commonly used for cases that follow the intravenous administration of calcium chloride and gluconate with extravasation (2,28,36-40). Nevertheless, this group also includes any calcinosis cutis induced by a iatrogenic cause. Therefore, causes and mechanisms as varied as the application of calcium chloride electrode paste (41-43), heel sticks in the neonatal period (5,44-47), or tumoral lysis due to hypercalcemia (48-52) can lead to this type of calcinosis.

CRITICISM ON THE CLASSIFICATION OF CALCINOSIS

Some criticism on etiopathogenic aspects

To summarize, this classification is based on the etiopathogenic background, i.e. a cause that may be metabolic, traumatic, iatrogenic, or unknown. However, one specific case can have more than one cause. In some cases of calcinosis cutis, for instance, more than one type of mechanism may be involved (53). Dystrophic and metabolic causes involved in the same case are not rare (54). There is a report on calcinosis cutis universalis (idiopathic *a priori*) associated with systemic lupus erythematosus (hypothesized as dystrophic) (55).

Iatrogenic calcinosis commonly refers to cases due to the intravenous administration of calcium chloride and gluconate with extravasation (28). Nevertheless, there are cases of dystrophic calcinosis in neonates following a single heel stick (5,44-47). Although dystrophic, this type is iatrogenic as well. Something similar happens with dystrophic calcinosis due to chronic needle trauma in patients with diabetes (56), which could be considered iatrogenic as well as dystrophic. The iatrogenic type of calcinosis in tumoral lysis is due to hypercalcemia, therefore, metastatic.

On the other hand, there are cases of cutaneous calcinosis following liver transplantation (57), which could therefore be considered as iatrogenic. Nevertheless, their pathogenic mechanism is unknown and some claim that it is dystrophic, while others claim it to be metastatic (57). However, since the ultimate mechanism remains "obscure", it would fit the definition of idiopathic.

Figure 5 shows an example of calcification on the post-mastectomy scar; although dystrophic, it could also be considered iatrogenic.

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The most complicated example of this interaction among several etiopathogenic mechanisms was a case of calcinosis in an 8-year-old patient (53) with a hyperphosphatemic stage due to the tumor lysis syndrome (metastatic). The patient developed calcification over a previous lesion of ecthyma gangrenosum (dystrophic), probably induced by an intravenous infusion of calcium gluconate (iatrogenic).

The fact that there are cases that are at the same time "several types of calcinosis" does not fit well any classification, where an entity should really be in one or in another group. Moreover, regarding the group of idiopathic calcinosis, the "unknown" reflects the lack of knowledge. Therefore, it is a concept that has been established from negative rather than positive connotations.

On the other hand, each group in the current classification has several subgroups, which are distinguished by criteria other than the physiopathologic ones, such as the location ("of scrotum"). Nonetheless, idiopathic calcinosis has not only been described in the scrotum, but in other genital areas such as the penis (58-60), or the vulva (61). Furthermore, in the literature, cases catalogued as "idiopathic calcinosis" have been described on the knee (62), or the neck (63). Although some have considered this type of calcinosis as secondary to epidermal cysts (64), immunohistochemical studies have failed to find cytokeratin deposits in the dermal tissue immediately adjacent to calcium deposits (65). On the penis, they have been considered as secondary to trauma or La Peyronie"s disease. Again, it is incompatible in a way with the designation "idiopathic".

Furthermore, many cases of familial tumoral calcinosis are no longer idiopathic, since genetic alterations under this condition are being identified. While in some cases, the genetic alteration causes hyperphosphatemia (66-68), in some others there is normophosphatemia (69). The latter is thought to be due to alterations in some genes involved in the regulation of extraosseous calcification (69). Therefore, while some should be placed in the group of metastatic calcinosis, some others might be dysthrophic.

Criticism on clinical aspects

The current classification of calcinosis mixes some clinical descriptions with etiopathogenic terms. For instance, terms as tumoral, scrotal, localized, or widespread describe locations, clinical appearance of the lesions or their distribution. The term "tumoral calcinosis" is found in the literature many times to refer to any large deposits of periarticular calcium. Nevertheless, strictly speaking, it should only refer to the entity described by Giard in 1898 (70) and by Duret in 1899 (71). To avoid this, some tried to distinguish between primary and secondary tumoral calcinosis (the former being either normophosphatemic or hyperphosphatemic) (72). This has, however, been strongly criticized by others (73).

Calcinosis universalis is a term meaning a wide extension of calcium deposits. It is commonly included in the group of idiopathic calcinosis, since the cause is not known many times. Some have hypothesized that some cases could be associated with

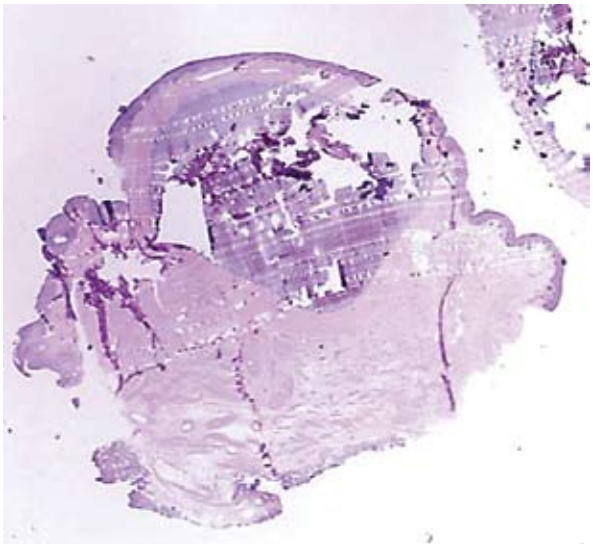

Figure 4. Calcinosis of scrotum in a 55-year-old man (HE; x2.5).

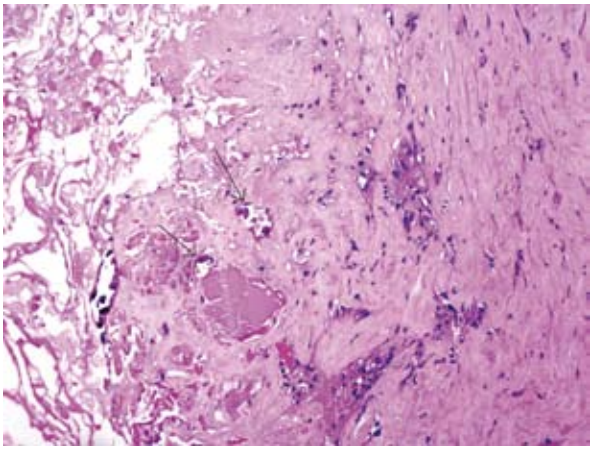

Figure 5. Calcification on the post-mastectomy scar in a 61-year-old woman. Although this type could be considered dystrophic, it could also be considered iatrogenic.

Non-calcified blood vessels in spite of the proximity of massive calcification (HE; x40).

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dermatomyositis that failed to be diagnosed in an acute phase (28,74). Nevertheless, there are cases of calcinosis universalis associated with well documented dermatomyositis (1), and therefore they are included in the group of dystrophic calcinosis.

Some new types of calcinosis have been described in the last decades. For instance, milia-type calcinosis was first described in 1978 (75). The term is based on the clinical aspect, resembling milia (76). Some cases are related to Down"s syndrome and premature aging has been suggested as a pathogenic mechanism (75). Nevertheless, since the cause is unknown, it would form part of the wide idiopathic group.

A classification of calcinosis from dermatopathologists?

What a dermatopathologist observes in a biopsy sample of any type of calcinosis are calcium deposits. Most times, the use of special stains is not even necessary for the diagnosis (Fig. 6). Some other findings, which explain such a deposit, can sometimes be recorded. For instance, a cyst or carcinoma would mostly explain the case as secondary dystrophic deposits.

Although calcium deposits always have the same aspect irrespective of the cause, the pattern of deposits varies depending on the cause. For instance, a deposit in arterial walls carries an ominous meaning many times, since it can be found in calciphylaxis, a life-threatening disease in patients with end-stage renal disease on dialysis (77). It has also been described in other circumstances such as cirrhosis (78), primary hyperparathyroidism (79-82), or malignancies (83-86). Therefore, since calciphylaxis can sometimes present in patients with preserved renal and parathyroid functions (87,88), the information from our reports can be the first data to trigger an alarm. Alerting the clinician on such a finding can lead to prompt treatment of the condition, which would otherwise be just interpreted as dystrophic or idiopathic calcinosis. Moreover, benign nodular calcification is a common condition in patients with chronic renal disease. Calciphylaxis is associated with high mortality, i.e. 1-year survival rate of 45% and 5-year survival rate of 35% (89-92).

On the other hand, it should be noted that calciphylaxis refers to the arteries; calcification of vein walls has been described as an iatrogenic effect of the administration of calcium chloride and sodium bicarbonate through a scalp vein needle (37). Venous calcification can also be seen in many organs as part of the aging process (Fig. 7).

Many times, a report of calcinosis cutis is followed by a study of the patient calcium metabolism. Metastatic calcinosis usually presents as a nodular (Fig. 8) or tumoral pattern (Fig. 9), with or without subcutaneous involvement. This pattern requires metabolic investigation. It is also a pattern found in connective tissues diseases. Therefore, clinical history can be oriented in this sense.

Tumoral pattern is seen in tumoral calcinosis, therefore, genetic investigations in the appropriate clinical context might be suggested when this pattern is found. On the contrary, idiopathic calcinosis due to extravasation of injected calcium products follows a widespread pattern (2,93), as it would be expected with a substance dissecting the connective tissue bundles.

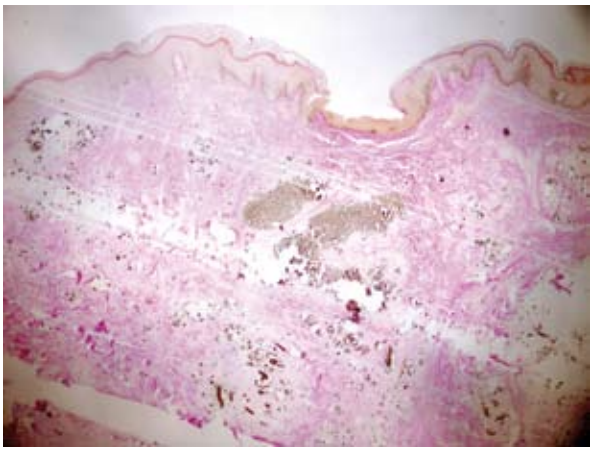

Figure 6. Von Kossa histochemichal staining showing calcium deposits in brown (HE; x2.4).

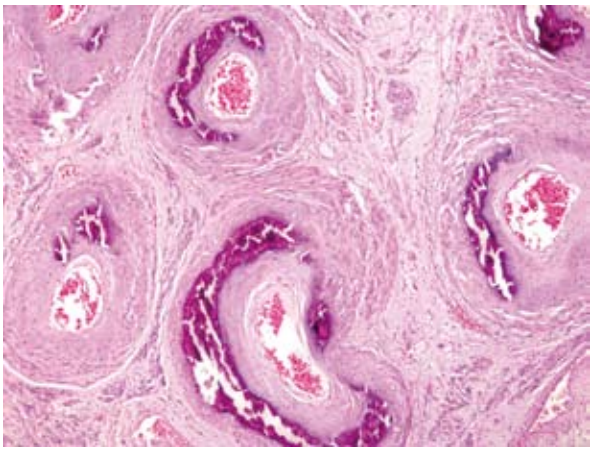

Figure 7. Venous calcification in the myometrium of a 75-year-old woman. This phenomenon is commonly seen as part of aging (HE; x40).

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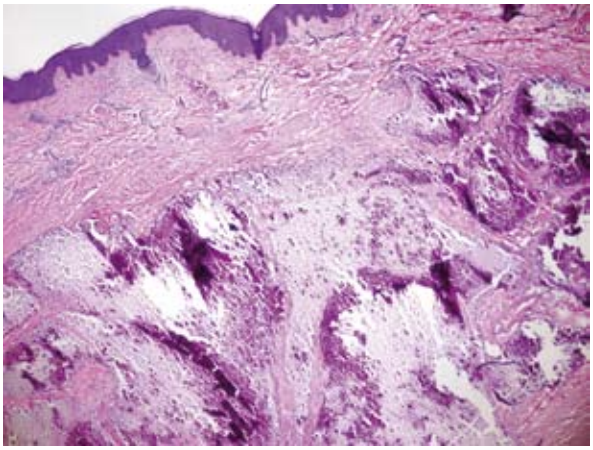

Figure 8. Nodular pattern of calcification found on the right buttock of a 75-year-old woman (HE, x10).

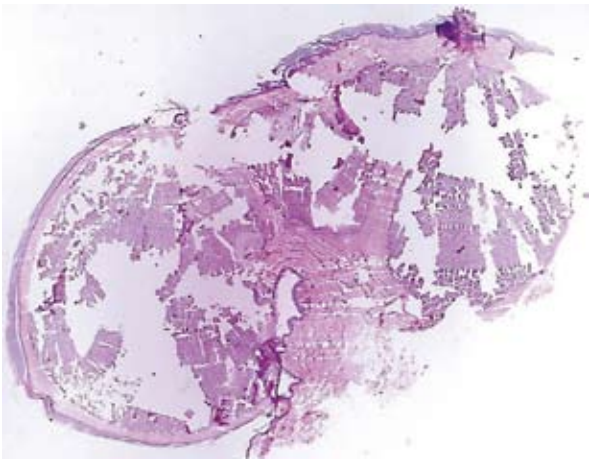

Figure 9. Tumoral pattern of calcification found on the shoulder of a 75-year-old woman (a different patient to the one presented in Fig. 8) (HE; x2.5).

Following these observations, a classification based on the morphological pattern of deposits could be as follows:

- without vascular involvement
  - small scattered deposits (Fig. 10 top, left)
    - Examples: calcinosis accompanying some tumors, cysts, local traumas
  - nodular and granular (Fig. 10 bottom, left)
    - Examples: idiopathic calcinosis of scrotum; calcified subepidermal nodule; milia-type calcinosis; connective tissue diseases (early)
  - tumoral (Fig. 10 bottom, right)
    - Examples: calcinosis of metabolic disorders; tumoral calcinosis; connective tissue diseases (advanced).
  - widespread dermal deposits (Fig. 10 top, right)
    - Examples: calcinosis cutis due to extravasation of calcium products
- with vascular involvement
  - calciphylaxis

We believe that this type of classification, or a similar one, simplifies the morphological information given to the clinician. It is also clear regarding the clinical action to follow.

The examples given in each group are, nevertheless, just examples. Some cases of calcification accompanying malformations or tumors, for instance, presented a nodular pattern (94). In such cases, morphological evidence of the subjacent malformation gives the clue.

At least, the overlapping between the groups, if any, is for sure much less than with the current classification.

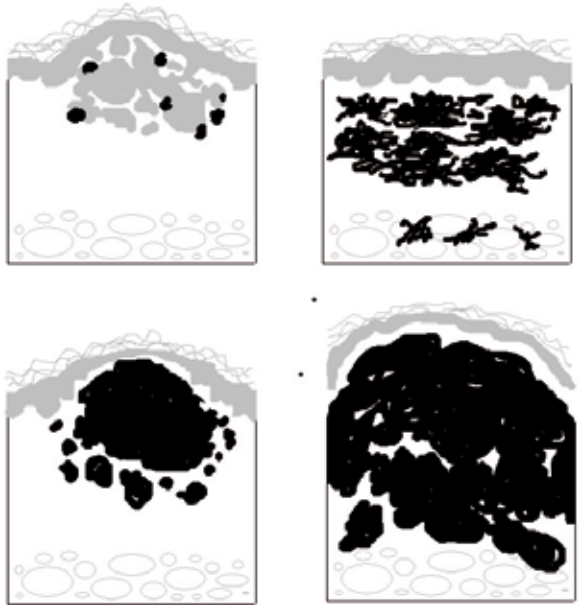

Figure 10. The four recognized patterns in this classification: small deposits (top left); widespread (top right); nodular (bottom left); and tumoral (bottom right).

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