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Original Article

Idiopathic Scrotal Calcinosis: Analysis of Epithelial Origin By Immunohistochemical Methods

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ABSTRACT

Objective: Scrotal calcinosis (SC) is a rare, usually asymptomatic, benign condition characterized by calcium phosphate deposition in the skin of the scrotum. The aim of this study is to investigate the clinical findings of patients diagnosed with scrotal calcinosis and to analyze the presence of possible epithelial origin by immunohistochemistry.

Methods: Fifteen patients diagnosed with scrotal calcinosis by excisional biopsy in two different centers between 2011 and 2020 were included in the study. Demographic, clinical, and laboratory data of the patients were obtained retrospectively from the electronic archive. Hematoxylin & Eosin (H&E) sections prepared from all cases were re-evaluated by two pathologists. Cytokeratin AE1-AE3 immunohistochemical stain was applied to 13 cases for the epithelium of the cyst.

Results: The median age of the patients was 32 (4–68). Patients had ulcer-free, white-yellow, painless nodules measuring 0.5 to 2 cm, mostly in the ventral part of the scrotum, and three had pruritus. Serum calcium levels were normal in eight patients. Histopathological examination showed amorphous and dense, H&E and basophilic calcium deposits with pseudocapsules in the scrotal dermis, most of which had no cyst walls or epithelization. While macrophage infiltration or hyalinization was observed around these areas, ossification was present in one case. While epidermal cysts were observed in the periphery in five cases, calcification, keratinization, and epithelial passage were observed together in two of them. In these areas, the cyst epithelium was positive with cytokeratin AE1-AE3 immunohistochemically. Cysts with cyst epithelium and calcification were smaller than those with only calcification.

Conclusion: Although the pathogenesis of idiopathic scrotal calcinosis is not clear, the cystic change and calcification in the cyst epithelium and the replacement of the epithelium by calcium appear to be the most likely mechanism after dilatation of the hair follicle.

INTRODUCTION

Scrotal calcinosis (SC) is a rare, usually asymptomatic, and sometimes recurrent benign condition characterized by calcium phosphate deposition in the scrotum skin.[1,2] Lewinsky first described the disease in 1883 as a subtype of calcinosis cutis.[3,4] Although scrotal calcinosis occurs predominantly in the third-fourth decades, cases affecting the adult and pediatric groups have been reported in the literature (9–85 years).[5] The pathogenesis of scrotal calcinosis is still a controversial issue. Dystrophic calcification of sebaceous cysts, degenerative changes in dartos muscle, calcification due to parasitic or foreign bodies, and adnexal tumors have been suggested in the etiology.[4,6] The literature on the subject of the study is limited to case reports and series due to the rare occurrence of the disease.

This study investigates the clinical findings of patients diagnosed with scrotal calcinosis and analyzes the presence of possible epithelial origin by immunohistochemistry.

MATERIALS AND METHODS

Fifteen patients diagnosed with scrotal calcinosis by excisional biopsy in two different centers between 2011 and 2020 were included in the study. The demographic, clinical, and laboratory data of the patients were obtained retrospectively by electronic archive scanning method. Hematoxylin & Eosin (H&E) sections (average five sections)

prepared from all cases were re-evaluated in terms of diagnosis and accompanying lesions by two pathologists (İ.Ö. and F.D.), who specialized in the field. Cytokeratin AE1-AE3 immunohistochemical staining (monoclonal DAKO) was applied to 13 cases to confirm the cyst epithelium.

RESULTS

The median age of the patients included in the study was 32 (4–68) years. There was no history of trauma, infection, or calcium metabolism disorder in the anamnesis of the patients. According to the examination findings, painless nodular masses with non-ulcerated sizes ranging from 0.5 to 2 cm were palpated in all patients, mainly in the ventral part of the scrotum, while three patients had additional complaints of itching. No skin fistulization or discharge was observed in any patient. Recurrent scrotal calcinosis was observed in two patients with similar signs and symptoms. When the laboratory analyzes were examined, it was found that serum calcium levels in eight patients were within normal limits. In the macroscopic examination of the excisional biopsies, hard, white-yellow, mostly nodular areas were observed. Histopathological examination of these areas revealed calcium deposits in the scrotal dermis, with pseudocapsular, amorphous, large, and dense character, basophilic stained with H&E, in most cases without any cyst wall or epithelization. While some of these calcification areas were surrounded by macrophage infiltration, some of them contained hyalinization areas without an inflammatory response (Figs. 1 and 2), ossification was present in one case. While multiple epidermal cysts (keratinous cysts) were observed close to calcification areas in five cases, calcification, keratinization, and epithelial passage were observed together in these epidermal cysts in two cases (Fig. 3). In these areas, the cyst epithelium was positive with cytokeratin AE1-AE3 immunohistochemically (Fig. 4). Cysts with combined cyst epithelium and calcification were in smaller foci compared to cysts with only calcification. In four cases, the cysts were close to the hair follicles. Cysts were not associated with the dermis in any of the cases. There was an increase in collagenization around some cysts.

DISCUSSION

Although scrotal calcinosis is generally a benign and asymptomatic disease, it may rarely recur, as in our two cases.[1,2] While pruritus was observed in three cases, most

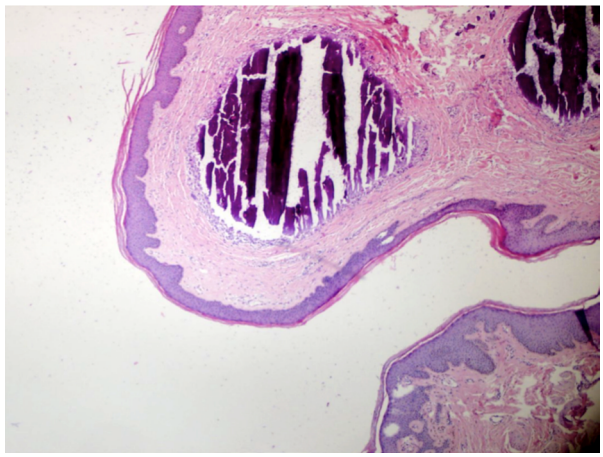

Figure 1. Dense, basophilic with H&E, and uniform calcium storage areas under the scrotal dermis x10.

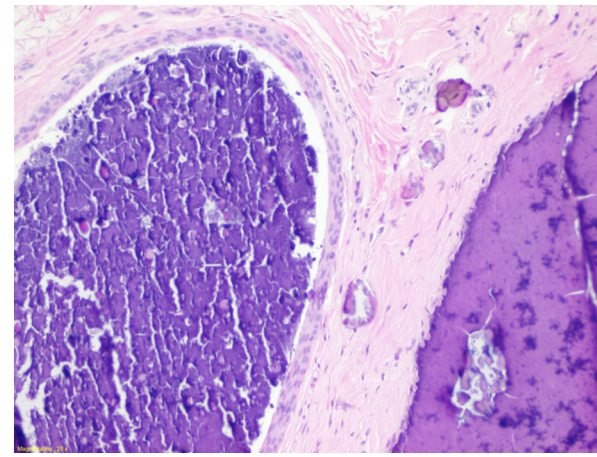

Figure 3. Calcified cyst area with cyst epithelium (left), and area of calcification without cyst epithelium (right) x20.

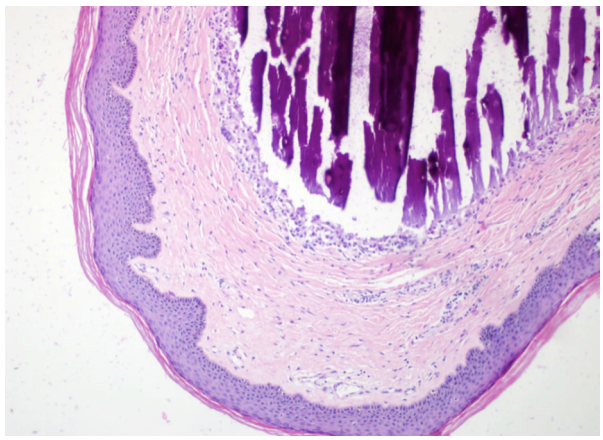

Figure 2. Basophilic calcium storage surrounded by histiocytes x20.

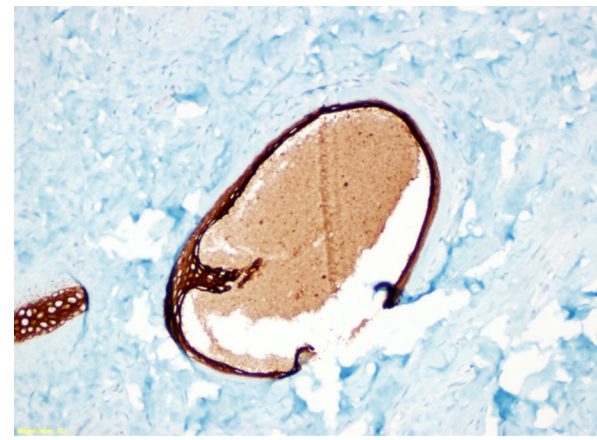

Figure 4. Immunohistochemically, epithelial Cytokeratin AE1-AE3 positivity in calcified cyst x20.

cases presented due to cosmetic concerns or a feeling of heaviness in the scrotum, as reported in the literature.[2] There is often no relationship with systemic diseases in etiopathogenesis, but local causes are emphasized, and no systemic disease relationship was found in our series.[4] While it may be confused with a lipoma on the patients' physical examination due to its white appearance, it may be confused with testicular tumors such as invasive teratoma and gonadoblastoma due to its calcification.[7] In our series, most of the cases were yellow-white, and were removed with a prediagnosis of lipoma. As in our study, the lesion size can vary from a few millimeters to a few centimeters.[8] Although connective tissue diseases such as scleroderma and dermatomyositis predisposed to calcinosis are also blamed in pathogenesis in the literature, these diseases were not present in our cases.[9] For diagnostic identification, the patient should have normal calcium-phosphate metabolism, no genitourinary infection, trauma, or any hormonal disease. In some reports, it has been suggested that recurrent minor chronic traumas maybe triggered by the process of scrotal shaving and hot shower, leading to occlusion of the hair follicle epithelium.[1,4] In our study, similar to Yiee et al.,[10] it was suggested that the presence of idiopathic calcinosis and scrotal cysts, mainly on the anterior surface of the scrotal skin, strengthens the possibility of recurrent minor trauma in the etiology. Dystrophic calcification of sebaceous cysts, degenerative changes in dartos muscle, calcification due to parasites or foreign bodies, and adnexal tumors have also been suggested in the pathogenesis.[4,6] Recently, however, the trend has shifted towards multiple epidermal cysts or sebaceous cysts that develop from the hair follicle, which calcifies due to the degenerative process following the infection and progresses with epithelial loss cyst wall over time.[4,5,7] In our series, the presence of multiple epidermal cysts in five cases supports the theory that the lesions developed from epidermal cysts. The coexistence of calcification and epithelization in two of these cases suggested that the epithelium was calcified secondary to the degenerative process. The smaller size of the epithelial cysts supported the theory that the lesions enlarge as the epithelium is replaced by calcification over time.[4,5,7] As in the literature, in our series, the lesions were microscopically in the form of calcified globules surrounded by lymphocytes, histiocytes, and hyalinization.[9] Although some authors suggest that sulfated mucopolysaccharides in exfoliated epithelium initiate calcification, there is no consensus on which type of cyst epithelium leads to calcification. In the examination of the cases in this study, we saw only epidermoid epithelium. Some authors reported that they observed hybrid epithelium from epidermoid to pilar epithelium in the cyst wall, while others reported the eccrine's origin.[4] However, as in many series, the cyst wall or epithelium could not be demonstrated in most of our cases.[11–13] In our case group, only two cases of cyst epithelium could be demonstrated with Cytokeratin AE1-AE3 immunohistochemical staining.[4] It has been reported in the literature that if small calcific foci are ignored during surgical excision, the possibility of recurrence will increase.[8] In our study, recurrent scrotal calcinosis was observed in two cases, and it was found as asymptomatic nodules.[9] Similar to the literature, no malignant transformation was observed in our cases.[14]

CONCLUSION

The pathogenesis of idiopathic scrotal calcinosis is still unclear. Dilatation of the hair follicle, subsequent cystic change in the follicle due to obstruction of the follicle opening, and subsequent replacement of the cyst wall epithelium by calcium appear to be the most likely mechanism. In order to reduce recurrence, cysts should be removed as well as calcification foci.

Clarification of etiopathogenesis with an extensive series will reduce recurrences and achieve better patient management results.

Ethics Committee Approval

This study approved by the Izmir Katip Celebi University Faculty of Medicine Non-Interventional Research Ethics Committee (Date: 18.02.2021, Decision No: 0072).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: İ.Ö.; Design: İ.Ö., F.U.D.; Supervision: İ.Ö., Z.A.Ö.; Fundings: İ.Ö., F.U.D, Z.A.Ö., M.O.H., F.C., I.G.; Materials: İ.Ö., F.U.D.; Data: İ.Ö., F.U.D; Analysis: İ.Ö., F.U.D., Z.A.Ö.; Literature search: İ.Ö., F.U.D., Z.A.Ö.; Writing: İ.Ö., Z.A.Ö.; Critical revision: İ.Ö., Z.A.Ö.

Conflict of Interest

None declared.

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İdiyopatik Skrotal Kalsinozis: İmmünhistokimyasal Yöntemlerle Epitelyal Kökenin Analizi

Amaç: Skrotal kalsinozis (SK) nadir görülen, genellikle asemptomatik, skrotum derisinde kalsiyum fosfat depolanmasına bağlı nodüllerle karakterize benign bir durumdur. Bu çalışmada amaç, skrotal kalsinozis tanılı hastaların klinik bulgularının araştırılması, immünhistokimyasal yöntemle olası epitelyal kökeni varlığının analiz edilmesidir.

Gereç ve Yöntem: Çalışmaya 2011–2020 yılları arasında, iki farklı merkezde, eksizyonel biyopsi ile skrotal kalsinozis tanısı alan 15 hasta dâhil edildi. Hastalara ait demografik, klinik ve laboratuvar verileri geriye dönük olarak elektronik arşivden elde edildi. Tüm olgulardan hazırlanan Hematoksilen & Eozin (H&E) kesitler iki patolog tarafından yeniden değerlendirildi. On üç olguya kist epiteli için sitokeratin AE1-AE3 immünhistokimyasal boyası uygulandı.

Bulgular: Hastaların ortanca yaş değeri 32 (4–68) idi. Hastalarda, skrotumun çoğunlukla ventral bölümünde non-ülsere, boyutları 0.5–2 cm arasında değişen beyaz-sarı renkte, ağrısız nodüller ve üçünde kaşıntı şikâyeti mevcut idi. Sekiz hastada incelenen serum kalsiyum değerlerinin normal idi. Histopatolojik incelemede skrotal dermiste psödokapsüllü, çoğunda kist duvarı ya da epitelizasyon izlenmeyen amorf ve dens, H&E ile bazofilik kalsiyum depozisyonları görüldü. Bu alanlar çevresinde yer yer makrofaj infiltrasyonu ya da hiyalinizasyon izlenirken bir olguda ossifikasyon mevcut idi. Beş olguda çevrede epidermal kistler izlenirken, ikisinde kalsifikasyon, keratinizasyon ve epitel geçişi birlikte izlendi. Bu alanlarda immünhistokimyasal olarak sitokeratin AE1-AE3 ile kist epiteli pozitif idi. Kist epiteli ve kalsifikasyon birlikte izlenen kistler, sadece kalsifikasyon izlenen kistlere göre daha küçük idi.

Sonuç: İdiyopatik skrotal kalsinoziste patogenez ile ilgili durum netlik kazanmamış olsa da kıl folikülünün dilatasyonu sonrası ağzının tıkanarak ilerleyen süreçte kistik değişim ve kist epitelinde kalsifikasyon ile epitelin yerini kalsiyumun alması en olası mekanizma gibi görünmektedir.

Anahtar Sözcükler: Kalsifikasyon; kalsinozis kutis; skrotum.