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Davetli Derleme /Invited Paper

Scrotal Calcinosis: A Case Report And Review Of Literature

Skrotal Kalsinozis: Vaka Sunumu ve Literatürün Gözden Geçirilmesi

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Skrotal kalsinozis (SK) skrotum derisinde çok sayıda küçük kalsifik nodüllerle karakterli, nadir görülen iyi seyirli bir hastalıktır. Nodüller zaman içinde sayıca ve boyut olarak artış gösterir. Hastalar genellikle uzun seneler bu hastalıkla yaşarlar ve kozmetik kaygıları dışında doktora başvurmazlar. Lezyonların histopatolojik incelemesinde, dermisde karakteristik amorf homojen kalsiyum depolanmaları içeren globuler bazofilik nodüller ve bunları çevreleyen histiositik dev hücrelerin eşlik ettiği kronik granülomatöz inflamasyon izlenir. SK gelişimine ait birçok hipotez ortaya atılmıştır. Bunların en popüler olanları epitelyal kist zemininde gelişmiş distrofik kalsifikasyon teorisi ile idyopatik etyoloji teorisidir. Bu yayında, tesbit edildiği andan itibaren 3 ay gibi kısa bir sürede hızla büyüyen skrotal nodüllere sahip 51 yaşında bir SK hastası sunmaktayız. Skrotal eksizyon materyelinin histopatolojik incelenmesinde, tipik SK lezyonlarına eşlik eden 3 adet küçük epitelyal kist ile bir kenarında epitel komponenti içeren 1 adet kalsifik nodül izlenmiştir. Bulgularımız, kalsifik nodüllerin epidermal kistlerin distrofik kalsifikasyonu ile geliştiği tezini destekler nitelikte olup, histopatolojik tablonun lezyonun yaşına göre değiştiği anlaşılmaktadır. Nodüllerin zaman içinde sayısının artması altta yatan nüks eden bir patolojinin varlığını düşündürmektedir. Bulgularımız, bu hazırlayıcı faktörün epitelyal kistler olduğunu düşündürmüştür. SK'de farklı safhalardaki lezyonların birlikte bulunması, sıklıkla kronik dönemde eksize edilmeleri nedeniyle de lezyonlarda epitelyal komponent izlenememesi şaşırtıcı bir bulgu olmamalıdır.

Anahtar Sözcükler: ***Kalsifikasyon, Kalsinozis, Distrofik, Skrotum***

Scrotal calcinosis (SC) is a benign disease characterized by multiple calcified nodules localized in scrotal dermis. Scrotal nodules develope slowly over many years and patients usually do not seek for treatment, until they care about their appearance. Histopathologic evaluation reveals multiple calcified nodules surrounded by a chronic granulomatous reaction including histiocytic giant cells. Numerous theories have been reported regarding the possible etiology of SC; the most popular ones including dystrophic calcification of preexisting epithelial cysts and purely idiopathic origin. We report a case of 51 years old man with a rapid onset and spreading scrotal nodules in a period of three months, and discuss whether SC is idopathic or not. We observed three epithelial cysts and a calcified nodule with partially epithelial lining. Our findings support the theory that SC is the result of the calcification of preexisting epithelial cysts. We think that histopathological findings vary with the age of the cysts, and there might be a repetitious cause which leads to new developing active lesions. It is not surprising that because the lesions survive for many years and the treatment is usually performed at late stages, lesions could not demonstrate epithelial component until there is a newly developing cyst.

Key Words: ***Calcification,Calcinosis,Dystrophic,Scrotum***

Calcinosis cutis, characterized by deposition of hydroxyapatite crystals of calcium phosphate in skin, is commonly encountered as a conseqence of connective tissue disease or metabolic abnormalities. However it could be idiopathic. There have been case reports of calcinosis cutis in various localizations, exhibiting none of preexisting metabolic or connective diseases. Calcified nodules in the labia majora of vulva (1), skin of penis (2), areola of nipple (3) and skin of scrotum (4-38) have been reported previously. SC, first described by Lewinsky in 1883 (4) is a rare benign condition characterized by multiple calcified nodules within scrotal dermis. There have been numerous theories about the etiology, including dystrophic calcification of epidermoid cysts and/or eccrine duct milia, degeneration of dartoic muscle, calcification secondary to minor trauma and idiopathic calcification within normal

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scrotal collagen. But the main debate focus on whether the calcifications were secondary to a preexisting epithelial cysts or they are truly idiopathic.

Case Presentation

We report patient a 51 year old male with a three month history of painless nodular lesions within scrotum which increased rapidly in number and size. He was not a smoker and had no history of trauma, surgery, inflammatory or metabolic disease, and drug abuse. None of the members of his family had such a complaint before. The lesions were palpable by physical examination and there were about 10 to 15 skin-colored nodules with 1,5 cm diameter. Ultrasonographic examination revealed multiple variable sized calcified nodules located in scrotal skin, without any calcification in testis. Biochemical parameters; serum calcium, calcitonin and parathyroid hormon levels, renal and liver function analysis, were within normal limits and no evidence of calcification was detected elsewhere. Urine analysis revealed 1000 mg/dl glucose in spot urine. The patient was treated by the excision of nodules en bloc above the Dartos facia with a horizontal section on the scrotal skin, under spinal anestesia. Primary closure was achieved without complication.

Material and Methods

Gross evaluation of the specimen revealed a scrotal skin material; 5,5 cm in length and 2,5 cm in thickness, exhibiting round firm nodules. On the cut surface there were 20 calcified nodules with yellowish white appearance measuring between 1 to 20 mm in diameter. Some of them included chulky material. Decalcification was performed and all of the lesions were serially sectioned, and histologically Hematoxylen-Eosin, Prussian Blue and Masson Trichrome stained slides were examined. Microscopic examination of the whole specimen revealed multiple calcified nodules, stained deeply basophilic with HE stain surrounded by a foreign body type chronic granulomatous reaction. All of the nodules were located within dermis, and an intact epidermis was overlying the lesions. Most of the nodules revealed similar appearance with more or less granulamatous reaction around them (Figure 1). However there were multiple punctate pure calcifications (Figure 2a), and large basophilic masses exhibiting compressed collagen of pseudocapsule (Figure 2b); without any accompanying inflammation, individually. Chronic granulomatous reaction composed of mostly epitheloid cells and giant cells with a lesser amount of lymphocytes. No organisms or parasites, and no hemosiderin was detected in the lesions. With serial sections we identified three small epithelial cysts with flattened stratified squamous epithelium and luminal keratin (Figure 3a-c), and a small hair follicle with some keratin in the center (Figure 4), without any calcification or inflammation, individually. Eventually we also managed to find an epithelial cyst, just beneath the epidermis, exhibiting calcification and granulomatous inflammation (Figure 5). Its epithelial lining of flattened stratified squamous cells was restricted to just one side of the nodule. Except this focus no definite epithelial lining was detected within or around any calcified mass.

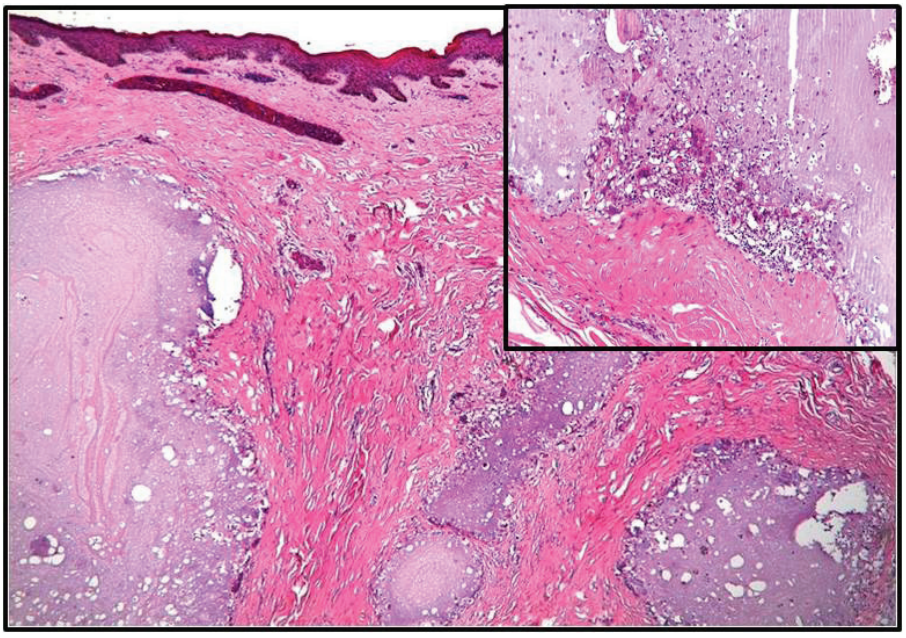

Figure 1: Multiple amorphous basophilic deposits of calcium without epithelial lining within dermis (Hematoxylin and eosin; original magnification x4). Note foreign body reaction showing numerous histiocytes (HE: x100, x200)

Discussion

SC is a rare benign disease characterised by cutaneous nodular calcifications in scrotal skin result from deposits of calcium and phosphorus. Scrotal nodules, typically begin to appear during childhood or early adulthood can be solitary or grouped, and they are usually bilateral. Pedinculated (5) or polipoid variants were also reported. Calcified nodules not only increase in number, but also become larger throughout life, and they may encircle almost entire scrotum. It is an exception that the lesions undergo spontaneous regression ; once reported by Hwang et al (6). While the lesions are initially skin-colored, they become yellowish as they grow. This process takes a long period of time that patients represent a history of slow growing nodules usually in a period of more than 10 years. The duration of the lesions varies from 3 months to 46 years in the literature (7,8). Our case is the second one (7) in the literature displaying a rapid growth within a period of three months from the date of onset. Most cases are as-

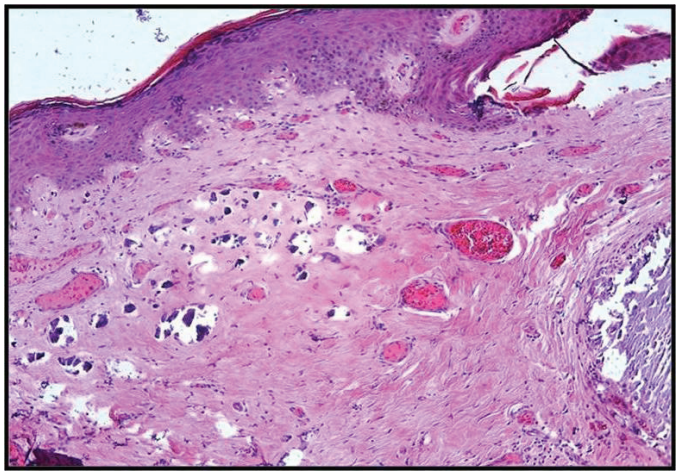

Figure 2a: Multiple small "buckshot" deposits scattered throughout the dermis (HE, x40)

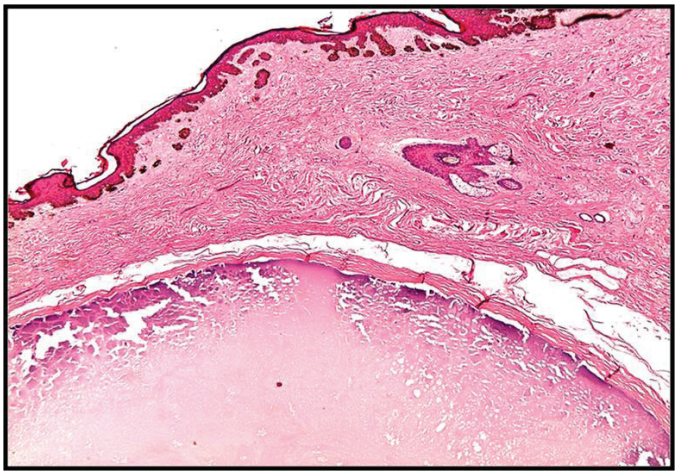

Figure 2b: A calcified nodule surrounded by a compressed collagen forming pseudocyst (HE, x40)

ympthomatic, and patients consult a physician if a secondary infection or discharging of chulky white material from the nodules develop which may be annoying. These complainments are occasional and patients usually do not seek medical help until they care about their external appearance that sometimes nodules become noticable even underneath the patient's underwear. Most of the patients consider the disease as a problem not for phyhsical health but particularly for their sexual activity which may lead to embarrassment and social problems. Chiummariello et al (9) reported a patient who did not seek treatment at any time during 42 years eventhough the lesions were aesthetically so unpleasant, untill he began a new relationship.

Because of the locality and the benign nature of the disease, treatment is recommended for only annoying symptomatic situations and aesthetic reasons. The treatment is always surgical. Removing these numerous lesions one by one is not recommended because of time wasting and potential of leaving relatively unaesthetic long scars. The most safe and effective surgical procedure for multiple nodules of the scrotum seems to be subtotal excision of the affected part of the scrotal skin above the dartos fascia. By the laxity of scrotal skin, en block excision with primary closure usually leads up to good cosmetic results without postoperative complications (10). There has also been an alternative method for the patients with limited number of lesions smaller than 4 mm, called "pinch and punch excision technique", that is similar with the "minimal excision tecnique" used for removing epidermoid cysts and steatocystoma multiplex (11). While some authors are convinced that surgery is curative, others insist on the high risk of relapse (10). Anyhow patients should be informed about the risk of recurrence, although it is rare. In the present case a follow up period of 3 months is not satisfactory to determine the recurrence.

SC is definitely diagnosed with histologic examination by a pathologist. The principal finding is the deposition of calcium in the dermis of the scrotum. Calcified nodules may be surrounded by histiocytes and an inflammatory giant cell reaction or may be surrounded by a fibrous capsule with no inflammation. Some of the nodules may exhibit epithelial structures in or around which makes observers think of a preexisting true cyst wall. The etiology of the SC is a very controversial issue. Numerous theories have been challenged to display the cause of the calcified nodules in the dermis. Calcification in the cutis is an evident fact which may progress in one of four major processes; dystrophic, metastatic, iatrogenic and idiopathic, according to the etiology (12). "idiopathic" term is used for the lesions with no definitively established etiologic factor such as tissue injury or systemic metabolic defect. Calcific process with the history of hypercalcemia and/or hyperphosphatemia, is generally attributed to "metastatic calcification". The most

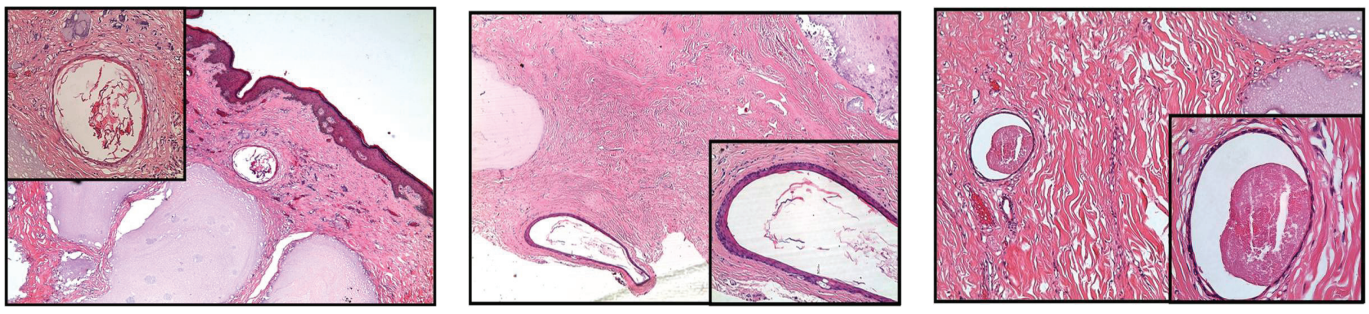

Figure 3a, b, c: Three of the epidermal inclusion cysts next to fully developed lesion of scrotal calcinosis. Note the flattened squamous epithelium and luminal keratin. (HE, x40, x400(inlet)

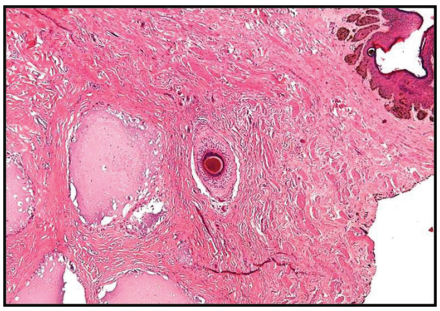

Figure 4: A dilated hair follicle with keratin plugging (HE, x40)

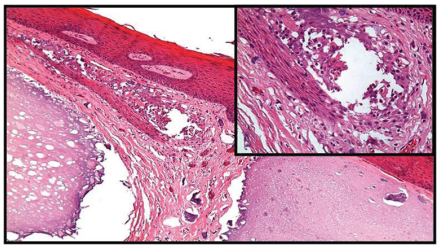

Figure 5: Calcium deposits partially lined by flattened stratified squamous epithelium. Resorption of the cyst wall and keratinous material by mononuclear inflammation and foreign body granuloma. (HE, x100, x400)

common form, "dystrophic calcification", implies an alteration in dermal collagen, induced by a predisposition like trauma, inflammation or collagen vascular disease, with normal calcium and phosphate levels in the blood. Literature revealed mostly single case reports, but series, consisting of 100 cases in the largest one (8), were also reported . However none of the reported cases showed abnormal calcium or phosphate levels in the blood chemistry. By positively exclusion of "metastatic calcification" theory the discusssion has made progress around "dystrophic" and "idiopathic" pathogenesis. While some authors believe it is truly idiopathic, others insist on dystrophic nature of the lesions with the evidence of preexisting epithelial structures in the nodules. But there is also a controversy between the authors who agree with the dystrophic process of the disease. The possible causes that may lead dystrophic calcification in the scrotal dermis were classified by Saladi et al (13) as; (i), calcific degeneration of epidermoid cysts ; (ii), dystrophic calcification of dartoic muscle and; (iii), calcification of ecrine sweat ducts. Although there have been relatively much support, few authors (14) believe that degeneration and necrosis of dartoic muscle, creating an acidophilic amorphous necrotic mass triggers the distrophic calcific process.

Role of epidermal cysts leads in the pathogenesis of SC. Most authors have documented that epithelial cysts themselves calcify and turn into calcified nodules (15, 16, 17, 18). In a study of Shah et al (15) with 20 SC cases; 14 patients revealed epidermal cysts with a variable amount of keratin and calcification in the vicinity of scrotal nodules, and 6 revealed nodules with abundant calcification and remnant epithelial structures in them. Swinhart and Golitz (19) observed epidermal cysts in three cases of SC; some were calcified with partial or total preexisting epithelial walls with an inflamatory reaction. Song et al (18) studied a patient with 51 scrotal nodules which 3 of epidermal cyts, 1 of calcified pilar cyst, 1 of calcified hibrid cyst, and the remaining indeterminate cysts some with calcification, and there were also purely calcified keratinous material associated with an inflammatory reaction and simple granular depositions of calcium within dermis. The largest study of SC, a combined prospective and retrospective study of 100 cases, conducted over a period of 15 years, was reported by Dubey et al (8). They detected a true cyst wall composed of compressed stratified squamous epithelium around calcium deposits in 60 of 100 patients. In the study the epithelium surrounded the deposits circumpherentially in 53, and partially in 11 cases. They stressed both the frequency of epithelial components especially accompanying with smaller nodules, and the naked appearance of larger nodules exhibiting pure calcification. Immunohistochemical (IHC) examination was also performed in the studies to make sure that the nodules have epithelial components in or around their content. Ito et al (16) reported a SC case originating from eccrine cysts with the support of IHC evaluation that revealed a positive reaction for CEA and EMA in the luminal cells and in the contents of a large cyst and ductal structures. Dini and Colafranceschi (17) also used antibodies against LMWCK, CAM5.2, cocktail of cytokeratin AE1/AE3 and CEA; and only a slight positivity for CK A1/A3 within one calcified nodule was observed within the whole lesion.

Diversity of the lesions directed the observers to suggest a multistage process for the development of clinically appearent SC from epidermal cysts. Swinhart and Golitz (19) targeted to inflammation of epidermal cysts as the initial event, and carried the process by order of dystrophic calcification of the cyst content, subsequent rupture of the cyst wall, a granulomatous proliferation, and with the cyst wall destruction remaining solely calcium deposits in the dermis in the end stage. Shah (15) and Song et al (18) defines a similar stepwise model with some discrapencies and details in each step. They presumed the presence of cystically dilated epidermal cysts or hair follicles with a variable amount of keratin in the center as early or precursor lesion. The next step is the development of head specks of calcification around and within this dilated follicle or the epidermal cyst. Shah et al (15) consider that the laxity or shaving of the scrotal skin causes tethering of hair follicles with obstructive cysts, and when these coupled with the warmer temperature, calcification occurs. As the calcification increases the epithelium starts to disappear, producing cystic calcified lesions. Epithelial remnants in the form of ghost squames or keratin flakes are seen within the lesions at this stage. They (15) proved the keratin flakes with CK stain by IHC. Calcific accumulation triggers a mononuclear inflammation and/or foreign body granuloma and the lesions are surrounded by foamy macrophages and foreign body giant cells which resorbe the cyst walls and of keratinous material. Finally with progressive calcification, total disappearance of the epithelial structures occur and large residual areas of calcification left behind with the classic picture of SC.

With the composition of the findings Song et al (18) implied that the keratin content might be more resistant to inflammation than the attenuated cell wall. In this way after the rupture of cysts, the resorption of the wall is rapid and calcified keratinous material surrounded by inflammatory cells may be seen even when the cyst wall could not be observed anymore.

On the other hand, some of the authors insist on the idiopathic origin because of the failure to show epithelial components even with IHC analysis. Wright et al (20); by performing antikeratin antibodies in multiple sections of 63 lesions from nine patients, couldn't show any epithelial structure in or around the calcified nodules. Karaca et al (21); also reported two cases with no remnants of epithelial cysts. Some other reports also emphasized the absence of true cyst wall (22,23). These authors concluded that SC is not a secondary phenomenon, and is truly idiopathic. There has been also a minority group of authors reporting different etiologic conditions such as; parasites (24), foreign body (4), various tumors (lymphangiomas, xanthomas, fibromas, teratomas or gonadoblastomas)(25), and repetative trauma caused by using tractor continuously as a farmer (26) were reported.

In the present case, it was realy confusing that although the lesions did not exist for a long period of time, we could hardly find just one focus of epithelial cyst wall within 20 nodules. Most of the nodules showed severe granulomatous reaction. Solely calcified nodules with fibrotic pseudocapsule were relatively rare. These findings support the hypothesis of Song et al (23) that the resolution of cyst wall occurs rapidly. We think that hence the calcification occurs, the epithelium disappears in a very short time, and the main process that takes time is the following steps. Whether the duration of lesions is short or long, if the observer defines an epithelial component in any of the nodules; then this lesion might be regarded as a newly developing epithelial cyst. It is clear that these lesions survive for many years, and certainly increase in number. There should be a repetitious predisposition, that we can observe both acute and chronic phases of the lesions simultaneously . Scrotum is a common site where multiple epidermal cyst occur, and we think that epithelial cysts may be the certain repetitious cause. The absence of epithelial component in the lesions should not exclude the possibility of preexisting epithelial cyst. Rather than this; the absence of epithelium may correspond to the entirely chronic phase of the nodules with no new developing lesion. It is considered particularly for long standing lesions. We refer a special histopathologic evaluation of the lesions with multiple serial sections to multiply the chance of finding an epithelial component in the nodules. Neverthless no epithelium may be observed. Hence, the term "idiopathic" should be used for cases demonstrating no tip lesion that would facilitate the ethiology even with serial multiple sections. On particular occassions with preexisting lesions; epithelial cysts or alternatives, dystrophic calcification would be related to the distinct etiology. But in our opinion the main debate should continue in the direction of what is the principle cause that gives rise to calcification of the epithelial cysts in the scrotum.

REFERENCES

1. Bernardo BD, Huettner PC, Merritt DF, et al. Idiaopathic calcinosis cutis presenting as labial lesions in children: report of two cases with literature review. J Pediatr Adolesc Gynecol. 1999; 12: 157-60
2. Lucke T, Fallowfield M, McHenry P. Idiaopathic calcinosis cutis of the penis. Br J Dermatol. 1997; 137: 1025-6
3. Oh CK, Kwon KS, Cho SH, et al. Idiopathic calcinosis of the areola of the nipple. J Dermatol. 2000; 27: 121-2
4. Shapiro L, Platt N, Torres-Rodriquez VM. Idiopathic calcinosis of the scrotum. Arch Dermatol. 1970; 102: 199-204
5. Schoeller T, Schubert HM, Wechselberger G. Idiopathic scrotal calcinosis – a pedinculated rare variant. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2008 April;61(4):466-7
6. C Hwang, Y J Kim, Y Lee, et al. Clin Exp Dermatol. 2009; 35: 159-60
7. J Hicheri, T Badri, B Fazaa, et al. Scrotal calcinosis: pathogenesis and case report. Acta Dermatoven APA. 2005; 14(2): 53-6
8. Dubey S, Sharma R, Maheshwari V. Scrotal calcinosis: Idiopathic or dystrophic? Dermatology Online Journal. 2010 Feb; 16(2): 5-
9. S Chiummariello, A Figus, G Menichini, et al. Scrotal calcinosis: a very rare multiple clinical presentation. Clin Exp Dermatol. 2009; 34: 795-7
10. Ruiz Genao DP, Rios-Buceta L, Herrero L, et al. Massive scrotal calcinosis. Dermatol Surg. 2002; 28: 745
11. Chang C-H, Yang C-H, Hong H-S. Surgical pearl: Pinch-punch excisions for scrotal calcinosis. J Am Acad Dermatol. 2004; 50: 780-1
12. Angamuthu N, Pais AV, Chandrakala SR. Calcinosis cutis: A report of four cases. Trop Doct. 2003; 33: 50-2
13. Saladi R N, Persaud A N, Phelps R G, et al. Scrotal calcinosis: Is tha cause still unknown? J Am Acad Dermatol. 2004; 51: 97
14. Pabuccuoglu U, Canda MS, Guray M, et al. The possible role of dartoic muscle degeneration in the pathogenesis of idiopathic scrotal calcinosis. Br J Dermatol. 2003; 148 :827-9
15. Shah V, and Shet T. Scrotal calcinosis results from calcification of cysts derived from hair follicles: A series of 20 cases evaluating the spectrum of changes resulting in scrotal calcinosis. Am J Dermatopathol. 2007 April; 29(2): 172-5
16. Ito A, Sakamoto F, Ito M. Dystrophic scrotal calcinosis originating from benign ecrine epithelial cysts. Br J Dermatol. 2001; 144: 146-50

17. Dini M, Colafrancesci M. Should scrotal calcinosis still be termed idiopathic? Am J Dermatopathol. 1998; 20: 399-402

18. Song DH, Lee KH, Kang WH. Idiopathic calcinosis of the scrotum: histopathologic observations of fifty-one nodules. J Am Acad Dermatol. 1988; 19: 1095-101

19. Swinehart JM, Golitz LE. Scrotal calcinosis: dystrophic calcifications of epidermoid cysts. Arch Dermatol. 1982; 118: 985-8

20. Wright S, Navsaria H, Leigh M. Idiopathic scrotal calcinosis is idiopathic. J Am Acad Dermatol. 1991; 24: 727-30

21. Karaca M, Taylan G, Akan M, et al. Idiopathic scrotal calcinosis: Surgical treatment and histopathologic evaluation of etiology. Urology. 2010 April 8

22. Mehregan AH. Calcinosis cutis: A review of the clinical forms and report of 75 cases. Semin Dermatol. 1984; 3: 53-61

23. Yahya H, Rafindadi AH. Idiopathic scrotal calcinosis: a report of four cases and review of the literature. Int J Dermatol. 2005 Mar; 44(3): 206-9

24. Browne SG. Calcinosis circumscripta of the scrotal wall. The etiological role Onchocerca volvulus. Br J Dermat. 1962; 74: 136-40

25. Saad AG, Zaatari GS. Scrotal calcinosis: is it idiopathic? Urology. 2001 Feb;57(2):365

26. Feinstein A, Kahana M, Schewach-Millet M, et al. İdiopathic calcinosis and vitiligo of the scrotum. J Am Acad Dermatol. 1984 Sep; 11(3): 519-20