Gigantic Idiopathic Scrotal Calcinosis: Can the Heat-Stress Protein-70 be Responsible for the Immunopathogenesis?: Case Report

Devasa İdiopatik Skrotal Kalsinozis: Isı-Şok Proteini-70 İmmünopatogenezden Sorumlu Olabilir mi?

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ABSTRACT Idiopathic scrotal calcinosis cutis (ISC) is a rare benign cutaneous disorder that consist of multiple calcified nodules within the scrotal skin. Pathogenesis of this condition is unknown. We presented a 41-year-old Caucasian man with a 20 year history of asymptomatic scrotal tumors, which had gradually increased in number. According to history, the patient was worked at a metalworking workshop for over 25 years, where he specifically has worked with big metal blocks by holding them between his legs in a hot environment. The histopathological examination showed amorph-basophilic-staining deposits of calcium crystal and a diagnosis of an ISC was made. In here, based on the interesting history of our patient and these findings, we tried to discuss that the lesions could have developed owing to the successive traumatic, thermal, chemical inflammation, and hypoxia through the heat-stress proteins (Hsp's). Written informed constent was obtained from the patient for publication of this report.

Key Words: Calcinosis; scrotum; etiology; heat-shock proteins; cell hypoxia

ÖZET İdiopatic skrotal kalsinozis kutis (ISK) skrotal deride çok sayıda kalsifiye nodüllerle karakterize nadir görülen benin bir deri hastalığıdır. Hastalığın etyopatogenezi bilinmemektedir. Bu makalede 20 yıldan beri sayıları giderek artan, asemptomatik skrotal tümörleri olan 41 yaşındaki bir erkek olgu sunulmuştur. Hasta, hikayesinde, 25 yıldan beri sıcak bir ortamda, özellikle büyük metal blokların bacaklar arasında sıkıştırılarak çalışıldığı bir hırdavat atölyesinde çalıştığını belirtiyordu. Histopatolojik incelemede, skrotal deride, amorf-bazofilik kalsiyum depozitleri gözlendi. Bu bulgularla ISK tanısı kondu. Bu makalede, hastamızın ilginç hikayesi ve elde edilen bulgular ışığında, lezyonların ısı-şok proteinleri (Hsp's) aracılığıyla, ardışık mekanik, termal ve kimyasal inflamasyon ve hipoksi nedeniyle oluşmuş olabileceğini irdelemeye çalıştık. Bu yayın için hastamızdan bilgilendirilmiş onam alınmıştır.

Anahtar Kelimeler: Kalsinoz; skrotum; etiyoloji; ısı-şok proteinleri; hücre hipoksisi

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Calcinosis cutis is a disorder of insoluble deposits of calcium in the dermis or subcutaneous tissue. There are mainly five forms: Metastatic, dystrophic, iatrogenic, calciphylaxis and idiopathic.[1,2] ISC is a common form of idiopathic calcinosis cutis.[1,3] Even though several mechanisms are discussed in the underlying pathological process, the exact cause of the disease is still unknown.[1,4,5]

CASE REPORT

A 41 year-old Caucasian man presented with multiple, asymptomatic, papular, and nodular lesions on the scrotum which had gradually increased in

size and number during the previous 20 years. There was neither history of any suggestive of sexually transmitted disease and other systemic, metabolic or inflammatory disorders, nor any iatrogenic, systemic or local drug administration. Also there was no family history of similar cutaneous lesions. However the patient has worked at a metalworking workshop for more than 25 years, where he specifically has worked with big metal blocks by holding them between the legs in a hot environment. On physical examination there were multiple reddish-brown, smooth-surfaced, firm, painless papules and nodules on the anterior and inferior surface of the scrotum. The lesional epidermis was dark-colored and hyperkeratotic. Size of the nodules, ranged from 2 to 28 mm in diameter. The biggest of these tumors was pediculated . There were no ulcerations on the lesions and no discharge on the scrotal skin (Figure 1a,b). The lesions were not tender, and the skin overlying the scrotum could be moved easily. However, the patient complained of poor image of the lesions and he stated that his sexual life has been affected negatively due to the lesions. The patient had a normal blood biochemical examination, which included calcium, phosphorus, thyroxine, triiodothyronine, thyroid-stimulating hormone, parathyroid hormone and had normal urinanalysis. On the gadolinium-enhanced magnetic resonance imaging (MRI), multiple low-signals were detected both on T1-Weighted (T1-W) (Figure 1c) and T2-Weighted (T2-W) (Figure 1d) strands at the scrotum which were interpreted calcified areas. One of the scrotal nodules was removed under local anesthesia for histopathologic examination. In histopathology, scrotal skin calcifications were noted. Epidermis was keratotic. There were numerous amorph-basophilic-deposits of calcium crystal without any surrounding epithelial lining or inflammation in the dermis, and dense fibrosis around of these deposits (Figure 1e,f). Based on these findings the diagnosis of an ISC was made. All lesions were

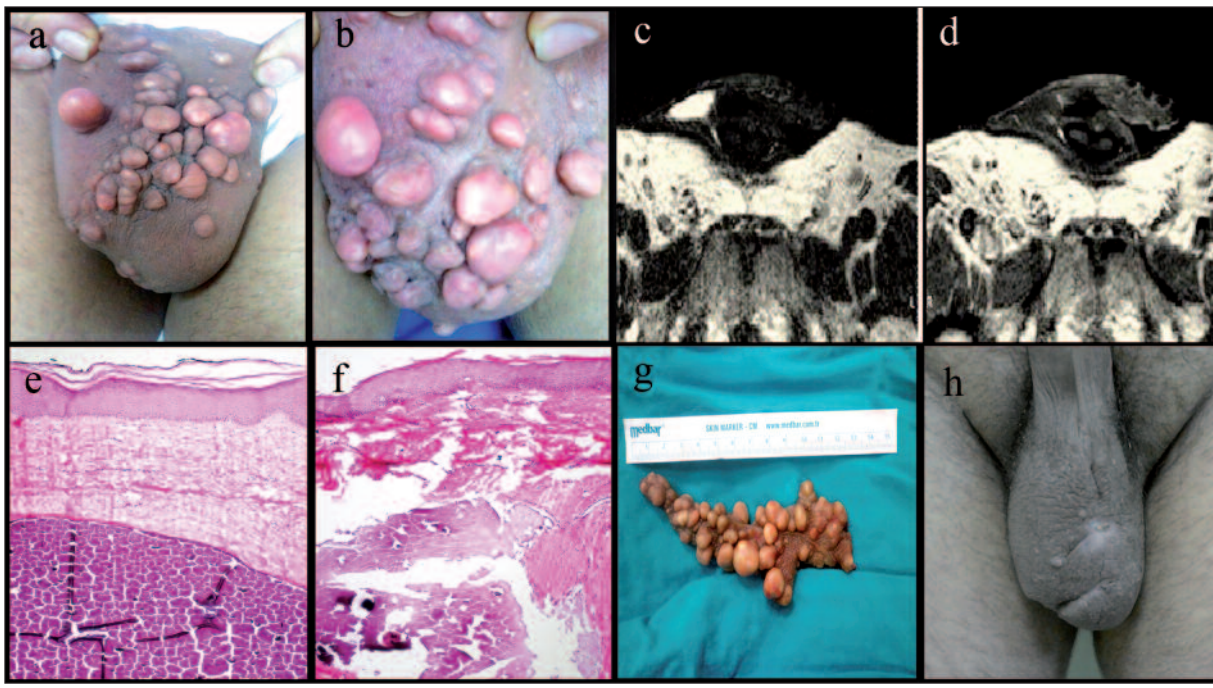

FIGURE 1: (a,b). Bilateral, multiple, reddish-brown, firm, gigantic subcutanous nodules and papules on the anterior and inferior surface of the scrotum. (distand **(a)** and closer **(b)** views). **(c,d).** Multiple low-signals both on the T1-W **(c)** and T2-W **(d)** strands with gadolinium-enhanced MRI at the scrotum. **(e,f).** The scrotal nodule showed increased epidermal keratinization, numerous amorph basophilic-staining deposits of calcium crystal without any surrounding epithelial lining or inflammation, and increased fibrous connective tissue in the dermis (HEx100 ve HEx200). **(g).** Postexcisional calcified scrotal spacemen. **(h).** Postoperative view of the scrotum 6 month after the primary closure.

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removed by subtotal excision of the scrotal wall under general anesthesia (Figure 1g). The excisional defect was closed with primary suture. No recurrence was observed after a 6-month follow-up period (Figure 1h).

DISCUSSION

Presentation of ISC is most common in the third decade of life, though patients commonly present lesions many years or decades after initial onset. The youngest reported patient was 9 years old and the oldest 85 years old. The nodules usually grow slowly over years to decades, but in multiple case reports they have been seen to develop more quickly.[5-9] Age of our patient and the developmental process of the lesions were consistent with those reported in the literature.

Clinical presentation of ISC consists of rock-hard nodules in the scrotal dermis. The size of nodules ranges from one milimeter to the largest reported presentation of 7 cm. These nodules are typically asymptomatic. Nevertheless, in some cases there may be also pruritus, perineal/suprapubic pain or white-chalky discharge. The patients seek medical advice usually for cosmetic reasons.[1,4,5,7] The appearence of the lesions and complaints of our patient were resembled those reported in the literature.

The exact cause of the ISC is still unknown.[1,4,5,7,10] However, considerable debate continues as to whether this term accurately uses. Some authors suggest that ISC is truly late presentation of ecrine duct milia or epidermal inclusion cysts while other claim that these lesions are caused by degenerated dartos muscle that have undergone dystrophic calcification.[1,8,11-14] Meanwhile, Carson draws attention to the possible role of nanobacteria in extraskeletal calcifications.[8]

In the history of our patient there were noticeable successive frictional trauma, exposure to metal dust, and hot enviroment. Two of the best known enviromental stresses are hypoxia and heat. To provide cellular adaptation to hypoxic stress conditions, many gene transcriptions occur. These transcriptions are controlled by a transcription factor called "hypoxia-inducible factor" (HIF).[15] Especially HIF-1 alpha subunit is stabilized by reactive oxygen species which are produced in hypoxic condition, and it provides the synthesis of many proteins by regulating the activation of around 70 genes.[15,16] Hsp's and antioxidant defense systems are responsible for cellular responses to stresses. Hsp response to hypoxia is provided through HIF.[17,18] The oxidative stress leads to increased Hsp's in the tissue. The proteins create a cellular response to many stressors such as exercize, heavy metals, chemical agents, oxidizing agents, ultraviolet radiation, and especially to the heat.[17] The stress proteins that are known to be inducible under the stress conditions such as hypoxia, exercise and increase in body temparature are members of the family of Hsp-70.[19-22] One of the mechanisms that is triggered by the enhancement of the Hsp's in the tissue is angiogenesis which is induced by vascular endotelial growth factor (VEGF). The process of angiogenesis continues until the desired oxygen level is achieved in the tissue.[23] On the other hand, Masaki et al. demostrated that increased reactive oxygen species led to a significant amount of increased intracellular calcium in the skin which was exposed to ultraviolet radiation.[24] Moreover, calcium salts are the ion compounds whose resolution increase with the increase in PH, and they precipitate in acidic tissue.[25,26]

In the light of this information, in our case, successive frictional trauma, high temperature of the working enviroment, and metal dust exposure which have lasted for many years, might have led to a chronic postinflammatory oxidative stress in the scrotal tissue. So, the stress might have led to a hypoxia and vasodilatation in the scrotal skin as well. As a result of this hypoxia, the increased reactive oxygen species might have increased intracellular calcium and tissue acitidy. On the other hand, these oxidative products also might have stimulated vascular angiogenesis by triggering the production of Hsp's, so the angiogenesis might have facilitated the mobilization of calcium to the traumatic skin. At the and of this process, increased calcium salts might have precipitated in the acidic tissue. Therefore, we thought that the scrotal cal-

cinosis in our case could not be truly idiopatic. These curious calcifications, with the help of the effect of the Koebner phenomenon, might have been formed due to the increasing, mobilizing and precipitating of the calcium salts in the postinflammatory damaged acidic tissue. Mechanisms that are suggested in this article have not been mentioned in previous reports of scrotal calcinosis.

In diagnosis imaging techniques such as radiograpy and ultrasonography can be used.[8,27] We preferred the gadolinium-enhanced MRI for diagnosis because of its superb soft-tissue contrast and multiplanar imaging capability, and it does not contain any radioactive risks. The calcium deposits are appear as low-signals both on T2-W and T1-W strands and we detected the same images with gadolinium-enhanced MRI at the scrotum as well.[28] To our knowledge, for the diagnosis of scrotal calcinosis, this technique has not been used previously.

Clinically, scrotal calcinosis may be confused with epidermal inclusion cyst, steatoma, soliter neurofibroma, ancient schwannoma, cutaneous horn, onchosercoma, and other benign tumors such as fibroma or lipoma.[8] The definitive diagnosis of ISC is based on pathognomic histological findings, which are calcified masses without a surrounding true cyst wall in the dermis as in our case. These findings differentiate ISC from calcified inclusion cysts and calcified onchocercal cysts as these conditions present with a true cyst wall.[1,5,8,12] On the other hand, when an epithelial-lined cystic space surrounds the calcium, supports an dystrophic etiology.[12,13] Evidence of inflammation including macrophages, mononuclear cells, and foreign body giant cells are commonly seen.[3,5,8,13] In our case there were not such inflammatory cells in the dermis, but there was increased epidermal keratinization on the especially lesional surface of the scrotum and significant dermal fibrosis. Hence, we thought that these findings could have been a result of the long-lasting chronic posttraumatic inflammation.

Treatment of the scrotal calcinosis is surgical.[3,5,7-9] Smaller lesions might be removed by novel pinch punch excision.[8] We preferred to remove of the lesions by subtotal excision of the scrotal wall since all lesions were localized in the same region.

In conclusion, we suggest that the family of Hsp-70 can be responsible for the immunopathogenesis of the scrotal calcinosis at least in some cases, triggered by successive mechanic, thermal and chemical stress. Our case study aims to draw attention to this rare disorder, and its probable etiopathogenetic mechanism emphasizing its relation with Hsp's. Unfortunately, so far not enough evidence has been collected to shed light on the underlying causes of the pathogenesis of ISC. We believe that new immunobiological research will be enlightening with regard to the pathogenesis of the disease.

REFERENCES

1. Cohen PR, Tschen JA. Idiopathic calcinosis cutis of the penis. J Clin Aesthet Dermatol 2012;5(12):23-30.
2. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: part I. Diagnostic pathway. J Am Acad Dermatol 2011; 65(1):1-12; quiz 13-4.
3. Lei X, Liu B, Cheng Q, Wu J. Idiopathic scrotal calcinosis: report of two cases and review of literature. Int J Dermatol 2012;51(2):199-203.
4. Walsh JS, Fairley JA. Calcifying disorders of the skin. J Am Acad Dermatol 1995;33(5 Pt 1):693-706; quiz 707-10.
5. Khallouk A, Yazami OE, Mellas S, Tazi MF, El Fassi J, Farih MH. Idiopathic scrotal calcinosis: a non-elucidated pathogenesis and its surgical treatment. Rev Urol 2011;13(2):95-7.
6. Gururajaprasad C, Nandini NM, Sunila. Idiopathic scrotal calcinosis--a case report. J Indian Med Assoc 2012;110(4):256-7.
7. Hoşcan MB, Akkaya H, Tunçkıran A, Durusoy C. Massive idiopathic scrotal calcinosis. Urology 2012;80(6):e71-2.
8. Tela UM, Ibrahim MB. Scrotal calcinosis: a case report and review of pathogenesis and surgical management. Case Rep Urol 2012; 2012:475246. doi: 10.1155/2012/475246
9. Saad AG, Zaatari GS. Scrotal calcinosis: is it idiopathic? Urology 2001;57(2):365.
10. Yusuf SM, Uloko AE, Sani MU, Mijinyawa SM, Mohammed AZ. Idiopathic scrotal calcinosis; a rare scrotal tumour: a case report and review of literature. Niger J Med 2010;19(4):482-4.
11. Akosa AB, Gilliland EA, Ali MH, Khoo CT. Idiopathic scrotal calcinosis: a possible aetiology reaffirmed. Br J Plast Surg 1989;42(3): 324-7.
12. Dare AJ, Axelsen RA. Scrotal calcinosis: origin from dystrophic calcification of eccrine duct milia. J Cutan Pathol 1988;15(3):142-9.

13. Swinehart JM, Golitz LE. Scrotal calcinosis. Dystrophic calcification of epidermoid cysts. Arch Dermatol 1982;118(12):985-8.
14. Dini M, Colafranceschi M. Should scrotal calcinosis still be termed idiopathic? Am J Dermatopathol 1998;20(4):399-402.
15. Wheeler DS, Wong HR. Heat shock response and acute lung injury. Free Radic Biol Med 2007;42(1):1-14.
16. Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003;3(10):721-32.
17. Chandel NS, McClintock DS, Feliciano CE, Wood TM, Melendez JA, Rodriguez AM, et al. Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1alpha during hypoxia: a mechanism of O2 sensing. J Biol Chem 2000;275(33): 25130-8.
18. Minet E, Michel G, Mottet D, Raes M, Michiels C. Transduction pathways involved in Hypoxia-Inducible Factor-1 phosphorylation and activation. Free Radic Biol Med 2001;31(7): 847-55.
19. Marber MS, Mestril R, Chi SH, Sayen MR, Yellon DM, Dillmann WH. Overexpression of the rat inducible 70-kD heat stress protein in a transgenic mouse increases the resistance of the heart to ischemic injury. J Clin Invest 1995;95(4):1446-56.
20. Paulsen G, Vissing K, Kalhovde JM, Ugelstad I, Bayer ML, Kadi F, et al. Maximal eccentric exercise induces a rapid accumulation of small heat shock proteins on myofibrils and a delayed HSP70 response in humans. Am J Physiol Regul Integr Comp Physiol 2007;293(2): R844-53.
21. Jiang H, He J, Pu S, Tang C, Xu G. Heat shock protein 70 is translocated to lipid droplets in rat adipocytes upon heat stimulation. Biochim Biophys Acta 2007;1771(1):66-74.
22. Liu JC, He M, Wan L, Cheng XS. Heat shock protein 70 gene transfection protects rat myocardium cell against anoxia-reoxygeneration injury. Chin Med J (Engl) 2007;120(7):578-83.
23. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Specialized tissues, stem cells, and tissue. In: Anderson M, Granum S, eds. Molecular Biology of The Cell. 5th ed. New York: Garland Science Taylor and Francis Group; 2008. p.1417-76.
24. Masaki H, Izutsu Y, Yahagi S, Okano Y. Reactive oxygen species in HaCaT keratinocytes after UVB irradiation are triggered by intracellular Ca(2+) levels. J Investig Dermatol Symp Proc 2009;14(1):50-2.
25. Karagülle O, Smorag U, Candir F, Gundermann G, Jonas U, Becker AJ, et al. Clinical study on the effect of mineral waters containing bicarbonate on the risk of urinary stone formation in patients with multiple episodes of CaOx-urolithiasis. World J Urol 2007;25(3): 315-23.
26. Goss SL, Lemons KA, Kerstetter JE, Bogner RH. Determination of calcium salt solubility with changes in pH and P(CO(2)), simulating varying gastrointestinal environments. J Pharm Pharmacol 2007;59(11): 1485-92.
27. Deganello A, Svasti-Salee D, Allen P, Clarke JL, Sellars ME, Sidhu PS. Scrotal calcification in a symptomatic paediatric population: Prevalence, location, and appearance in a cohort of 516 patients. Clin Radiol 2012;67(9): 862-7.
28. Oot RF, New PF, Pile-Spellman J, Rosen BR, Shoukimas GM, Davis KR. The detection of intracranial calcifications by MR. AJNR Am J Neuroradiol 1986;7(5):801-9.