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TITLE: CREST SENDROMU VE BÖBREK TUTULUMU

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PAGES: 186-189

ORIGINAL PDF URL: <https://dergipark.org.tr/tr/download/article-file/2545>



CASE REPORT

CREST SYNDROME AND RENAL INVOLVEMENT

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ABSTRACT

A 66 year-old woman with a history of Raynaud's phenomenon for 30 years, presented with fingertip calcification and ulceration. She complained of discharge of small stones from these ulcerated lesions for several years and dysphagia in the past year. On physical examination, we noticed mild telangiectasias on her face. Calcifications were observed on her foot and hand radiographs. Laboratory findings revealed normal Ca⁺⁺ and PO₄, but the serum parathyroid hormone level was elevated on two occasions. Anticentromer antibody and ANA were positive, whereas anti-Scl 70 was negative. At gastroscopy, esophageal aperistaltism was found and esophagogastroduodenography(EGDG) was suggested. Esophageal dysmotility was found in EGDG and with these findings we decided the patient had CREST syndrome. Hyperparathyroidism was thought to be secondary to calcinosis cutis. We know that during the progression of this disease, the calcinosis type of systemic sclerosis can be characterized by renal involvement and secondary hyperparathyroidism, but it is rarely seen with the CREST syndrome. Because the CREST syndrome is a slowly progressing disease, we believe hyperparathyroidism in this patient developed after many years of hypertension due to the renal disease.

Keywords: CREST syndrome, Renal involvement, Scleroderma, Hypertension

CREST SENDROMU VE BÖBREK TUTULUMU

ÖZET

Otuz yıldır Raynaud's fenomeni tanısı olan 66 yaşındaki kadın hasta, parmak uçlarında kalsifikasyon ve ülserasyon şikayeti ile başvurdu. Bu ülser bölgelerden küçük taşların koparak düştüğünü ifade ediyordu. Son yıllarda disfaji şikayeti de gelişen hastanın fizik muayenesinde yüzünde telenjiaktazileri mevcuttu. El ve ayak grafilerinde kalsifikasyonlar gözlemlendi. Kan tetkiklerinde kalsiyum ve fosfor düzeyleri normal ancak iPTH yüksekti. Anti-Scl 70 antikoru negatif iken ANA ve Anti-sentromer antikoru pozitif bulundu. Gastroskopisinde ösefagial aperistaltizm gözlemlendi ve Ösefagus-Mide-Duedonum(ÖMD) grafisi planlandı. ÖMD'de ösefagial dismotilitenin varlığı, hastada CREST sendromu olduğunu kanıtlıyordu. Hiperparatiroidinin ise kalsinozise ikincil geliştiği düşünüldü. Progresif Sistemik Sklerozisin kalsinozis tipinde böbrek tutulumu ve sekonder hiperparatiroidi geliştiği bilinmektedir. Ancak CREST sendromu çok yavaş ilerleyen bir hastalık olduğundan sekonder hiperparatiroidizm çok nadiren görülür. Vakamız bu açıdan nadir görülen, böbrek tutulumu ve hipertansiyon ile giden CREST sendromu olarak değerlendirildi.

Anahtar Kelimeler: CREST sendromu, Hipertansiyon, Skleroderma, Böbrek tutulumu

INTRODUCTION

CREST syndrome is a limited type of scleroderma which includes Calcinosis cutis,

Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly and Telangiectasia. Patients with CREST syndrome are typically women and are older

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Marmara Medical Journal 2007;20(3);186-189



than patients with systemic scleroderma (SSc) with a long history (10-15 years) of Raynaud's phenomenon; skin involvement is limited to the digits or hands, face, feet and forearms; nail fold capillary dilatation; and early onset of facial and digital telangiectasias. Also, there is a high incidence (70-80%) of anticentromere antibodies (ACA) in CREST, whereas Scl-70 is more frequently associated with SSc¹.

Renal involvement and secondary hyperparathyroidism has previously been reported, mostly in SSc, but can also rarely occur in the CREST syndrome² which is known as "scleroderma renal crisis" or "scleroderma kidney". J.Serup and H.K. Hagdrup³ reported that secondary hyperparathyroidism is common in patients with aberrant calcifications as a regulatory mechanism to maintain a normal calcium concentration in the blood. But there were no differences in the levels of total calcium, phosphate, magnesium, alkaline phosphatase, acid phosphatase, albumin and serum creatinine.

CASE REPORT

We report a 66-year-old woman who had initially presented with Raynaud's phenomenon 30 years previously. Her complaint usually occurred on cold days or in cold water, initially presenting as pale and cold digits which progressed to painful, purple finger tips. In the last 10 years, first she began having fingertip ulcerations and perforations, then the same symptoms began in her toes. She noticed that some small things like stones came out of these very painful ulcerations, which healed slowly. In addition, she complained of dysphagia and heartburn in the last year. The patient had had hypertension for 5 years regulated with Verapamil at 120 mg /day.

On physical examination, her blood pressure was 150/90 mmHg, and her heart rate was 94/min. Skin hardness and thickening were palpated at the volar faces of the hands and toes. There was a hard, hyperkeratotic, round lesion (0.5cm in diameter) on the left hand third phalanx volar face and another round

hyperkeratotic lesion (1 cm in diameter) on the left foot first phalanx volar face, from which the patient reported that a small stone and suppuration had recently discharged (Figure 1). In addition, we noticed clubbing and flexion-like shape deformation of the fingers, but typical sclerodactyly was not found.



Figure 1: Round hyperkeratotic lesion at the left foot first phalanx volar face

Radiographs of bilateral hand and foot showed remarkable cutaneous calcifications, especially near the fingertips (Figure 2). On skin biopsy; epidermal hyperkeratosis, irregular acantosis and connective tissue increment in the dermis were seen. A deep biopsy performed from the calcinosis seen in the left hand radiogram revealed calcification.

In laboratory findings, the Ca⁺⁺ level was mildly elevated once (10.6mg/dl) but on follow-up turned to normal levels. Alkaline phosphatase and PO₄ levels were in normal ranges. The parathyroid hormone was checked for differentiation of calcinosis cutis and was found to be high (218.4pg/ml, 15-65 pg/ml normal ranges) on two occasions. Mg was mildly high (2.6 and 2.8mg/dl; 1.8-2.5 normal ranges), CRP and Romatoid Factor (RF) were positive; ESR was 31mm/h. Blood urea level was elevated (45.5 mg/dl; 12.6-42.6



normal ranges) but creatinin level was normal. According to these findings, we suspected the patient had CREST syndrome or systemic scleroderma. As we expected, the anti-centromere antibody and anti-nuclear antibody (ANA) were positive, whereas anti-Scl 70 and anti-ds DNA were found negative.



Figure 2: Cutaneous calcifications (arrows) near the first fingertip of the left hand on the radiogram

We thought that hyperparathyroidism could have developed secondary to calcium deposition or to primary hyperparathyroidism, thus we tested 24 hour urine Ca^{++} and creatinine clearance. Urine Ca^{++} was normal (121mg/d; normal ranges 100-300mg/d) but creatinine clearance was found low (31ml/dk). These results led us to the conclusion that hyperparathyroidism may have been secondary to renal failure, which can be renal involvement due to the CREST syndrome.

We planned a gastroscopy and eosophagogastroduodenography (EGD) because of dysphagia. In gastroscopy, aperistaltic eosophagus, hiatal hernia and pyloric dysfunction were found. In EGD, eosophageal dysmotility was observed.

In conclusion, we decided that this patient had CREST syndrome. We know that in the

CREST syndrome, pulmonary hypertension and biliary cirrhosis may appear, so an echocardiography was performed and pulmonary pressure was found in the normal range. In the laboratory findings, no problem with hepatic function appeared. As treatment for CREST, the patient was put on 100mg/day D-Penisillamine and 30mg/day Nifedipin.

The patient was informed about this rare disease and an informed consent form was signed by her.

DISCUSSION

Calcification of the skin may occur in all forms of SSc, but is most commonly seen as part of the CREST syndrome. Generally, dystrophic calcification associated with massive collagen degeneration results in calcinosis⁴. The mineral deposits in dystrophic calcinosis cutis secondary to the CREST syndrome have been identified as amorphous calcium hydroxy-apatite^{5,6}. The pathogenesis of calcinosis is not well understood, but the calcium can ulcerate the skin, be expelled as chalky material and cause recurrent episodes of local inflammation⁷. This calcification is associated with an underlying tissue abnormality and collagen degeneration allows increased intracellular calcium influx⁸.

The calcinosis type of systemic sclerosis is characterized by secondary hyperparathyroidism developed during the progression of the disease. Secondary hyperparathyroidism is common in systemic sclerosis, in particular in patients with aberrant calcifications, usually with normal calcium and phosphate plasma levels. During the disease, in order to maintain a normal calcium concentration in the blood, secondary hyperparathyroidism develops³.

Progressive systemic sclerosis is frequently associated with renal involvement. This complication is characterized by the sudden onset of severe arterial hypertension and untreated hypertension is followed by rapidly progressive oliguric renal failure ("scleroderma kidney" or "scleroderma renal crisis")⁹. But such extensive changes are



unusual in patients with the CREST syndrome.

Steen VD et al² found that 18% of the patients having systemic scleroderma and only 1% of the patients who classified as having the CREST syndrome variant at the time of onset of “scleroderma renal crisis”. All these persons had telangiectasiae but not calcinosis of the fingers. In most patients, renal crisis developed early during their illness and no patient with renal disease had a serum creatinine value greater than 1.3mg/dl. According to this study, isolated mild hypertension does not serve to predict subsequent development of “scleroderma kidney” and is probably not etiologically related to the renal vascular abnormalities of progressive systemic sclerosis. But there is still some disagreement concerning the frequency of arterial hypertension in patients with progressive systemic sclerosis and the question of whether or not this finding alone comprises evidence of renal involvement.

Four months after the beginning of the treatment, the calcium ion level had returned to normal ranges in our patient. Some of the patient's complaints had decreased. This led us to believe that hypercalcemia was related to the CREST syndrome and had developed in consequence of secondary hyperparathyroidism. Mild hypermagnesemia continued although we could not find any reason or relation to the disease.

We did not perform a renal biopsy on the patient but we found some laboratory findings which supported probable renal involvement, which is very rare in the CREST syndrome.

This case may be an important guide concerning the follow-up of patients with the CREST syndrome, which is rarely seen together with severe calcinosis, renal failure and hyperparathyroidism.

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