

Calcinosis Cutis in a Patient With Eosinophilia-Myalgia Syndrome: Case Report

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Eosinophilia-myalgia syndrome (EMS) often is a disabling disorder caused by the consumption of contaminated L-tryptophan. Affected patients present with an array of symptoms, including cutaneous manifestations, peripheral eosinophilia, myalgias, and long-term neurocognitive disability. This article is the first reported case of a patient with EMS who developed calcinosis cutis. While many long-term sequelae of EMS are reported in the literature, there are no reports of the development of dystrophic calcification in these patients. The calcinosis cutis in this patient with EMS may represent a new manifestation of EMS that has not been documented to date. If more patients with EMS develop calcinosis cutis, it will present a therapeutic challenge to the physicians managing these patients.

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Eosinophilia-myalgia syndrome (EMS), first described in 1990,¹ is a systemic illness characterized by peripheral eosinophilia of greater than 1000 cells/mm³, severe myalgias, and the exclusion of infectious or neoplastic processes that may account for these findings.² Belongia et al² conducted epidemiologic analysis of patients presenting with EMS and found L-tryptophan, specifically L-tryptophan manufactured in one plant, to be the etiologic factor. The clinical manifestations vary but often include cutaneous abnormalities, severe myalgias, neuropathies, neuromuscular abnormalities, cardiopulmonary disease, gastrointestinal disease, articular pathology,

and neuropsychiatric disease. Eighty-seven percent of patients with EMS have cutaneous manifestations ranging from alopecia to eosinophilic fasciitis or diffuse or localized scleroderma.^{3,4} To date, the literature documents no patients with EMS developing calcinosis cutis. We report one case of calcinosis cutis in a patient with EMS. The patient had calcinosis in areas of sclerosis and induration on the elbows, forearms, hips, and buttocks. This finding presents a therapeutic challenge to physicians managing patients with EMS.

Case Report

A 78-year-old white woman with a history of EMS diagnosed in 1990 presented with a chief complaint of “pebbles under my skin.” The lesions first appeared on the extensor surfaces of the elbows and forearms and progressed to her hips and buttocks. She was told that she had subcutaneous calcium after a wrist radiograph in 1999, but the hard papules emerged 3 years after the radiograph. Her digits were not affected. These hard nodules were located in areas of residual sclerosed skin secondary to her EMS. She complained that the nodules caused a moderate amount of pain, and they often ulcerated and failed to heal. The ulcerated areas occasionally oozed serosanguinous exudate, and her clothing often was stained by the discharge. She tried silver sulfadiazine cream with no relief. She denied Raynaud phenomenon, past or present. She had no family history of rheumatic disease or calcinosis cutis.

Her medications included alendronate sodium 70 mg/wk, raloxifene hydrochloride 60 mg/d, and calcium citrate 400 mg twice daily for osteoporosis. She had been taking calcium citrate for at least 5 years, and she started taking alendronate sodium in January 1998. Raloxifene hydrochloride was added to her treatment regimen in January 2000. She had no known drug allergies.

Her past medical history indicated EMS and osteoporosis. She was diagnosed with EMS after

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Figure 1. A pitting scar with residual chalky residue in an area of sclerosed skin on the forearm. Hard discrete 2- to 5-mm papules surround the scar.



Figure 2. Patchy calcifications extending from subcutaneous tissue to the dermis.



developing severe myalgias, skin puckering, non-pitting edema, and a peripheral eosinophilia of 46%. She had a cutaneous biopsy of an area of skin puckering that showed eosinophilic fasciitis. After further questioning, we learned that she had taken vitamins that contained L-tryptophan. At the time of diagnosis, she also suffered from alopecia and peripheral neuropathy. Her eosinophilia, alopecia, and neuropathy resolved with oral corticosteroids, but she continued to suffer from myalgias and cutaneous sclerosis and induration of the forearms, lower legs, and lateral hips.

Physical examination revealed indurated plaques on the extensor surfaces of the elbows, forearms (Figure 1), hips, and buttocks. Within the sclerotic and indurated skin, hard and chalky 2- to

5-mm nodules were scattered. The sclerotic plaques on the hips contained ulceration with a dark sero-sanguinous exudate. She also had areas of induration in the pretibial area bilaterally, but these sclerotic areas did not contain hard nodules.

Laboratory investigation revealed her complete blood count, blood chemistry, serum thyrotropin, and liver function tests to be within reference range. Antinuclear antibodies and scleroderma antibody-70 were within reference range. Radiographic examination of her pelvis revealed patchy calcifications in the subcutaneous tissue (Figure 2).

Comment

EMS was first recognized in 1990 when approximately 1500 patients who had taken L-tryptophan

were found to have a constellation of clinical manifestations.¹ After a mean latent period of 84 days, patients developed an acute syndrome manifested by sudden severe myalgias, fever, cough, and dyspnea; a faint maculopapular rash; and cutaneous edema.³ Eosinophil counts rose to a mean of $6.3 \times 10^9/L$.³ After a period of weeks to months, most of the early symptomatology resolved and eosinophil counts returned to baseline. However, most patients continued to suffer from severe myalgias and peripheral neuropathies, and skin thickening or sclerodermatous changes were seen in 33% of patients.⁵ Months to years later, up to 62% of patients with EMS developed neurocognitive dysfunction.⁶

Kaufman et al⁵ documented cutaneous manifestations in 26 patients (87%) with EMS. At presentation, these patients generally complained of faint erythematous macular eruptions, nonpitting edema, alopecia, and pruritus. In one series, 13 patients (43%) initially complained of a diffuse erythematous macular rash on the trunk and 3 patients (10%) complained of multiple ecchymoses. These manifestations resolved over a period of months, but 16 patients (53%) developed nonpitting edema.⁵ Three to 6 months after patients discontinued taking L-tryptophan, chronic skin changes developed, resembling scleroderma. Nine patients (33%) developed induration and puckering of the skin, accompanied by skin thickening. Although the findings resembled those of eosinophilic fasciitis, only 4 patients (13%) were diagnosed with eosinophilic fasciitis as a component of their EMS. The remaining patients presented with cutaneous manifestations resembling diffuse or localized scleroderma. Thus, up to 15 patients (50%) with EMS developed eosinophilic fasciitis and/or sclerodermatous skin changes.⁵

Pseudosclerodermas are skin diseases of unrelated etiology with induration of the skin resembling scleroderma, either localized or systemic. Histologically, the pseudosclerodermas have marked dermal or subcutaneous fat fibrosis.⁷ The histology of EMS patients with skin induration and thickening typically reveals cutaneous and subcutaneous fibrosis with marked collagen deposition. The dermal thickening and collagen infiltration of chronic EMS has been described as identical to scleroderma or morphea.⁸ Dermal fibroblasts in patients with EMS synthesize collagen at a rate of up to 3 times normal controls.⁹

Up to 10% of patients with systemic sclerosis develop calcinosis cutis, and there have been reports of patients with localized scleroderma developing calcinosis and subsequent ulceration.^{7,10,11} Despite the histologic clinical resemblance to

sclerodermatous skin disease, to date, this case represents the first documentation of such changes occurring in a patient with EMS.

There are 4 types of calcinosis cutis: metastatic, idiopathic, iatrogenic, and dystrophic.¹² Metastatic calcification occurs when there is a defect in calcium and phosphate regulation or metabolism, which results in calcium deposition in normal tissue. In this case, calcification often affects the blood vessels, kidneys, gastric mucosa, and lungs.¹² When no disorder of calcium or phosphate metabolism is identified and calcium deposits are present in normal tissue, the cause is classified as idiopathic.¹² Iatrogenic calcification is a recognized complication of intravenous calcium chloride administration as well as calcium gluconate administration. Iatrogenic calcification also occurs in areas of trauma and in some patients with a history of extensive contact with calcium salts.¹² Generally, the anatomic location of iatrogenic calcification is on an extremity, proximal or distal to the intravenous catheter.¹³ Dystrophic calcification, the most common cause of calcinosis cutis, occurs in patients with normal calcium and phosphorus levels who have areas of tissue damage like with dermatomyositis or connective tissue disease.¹²

In our patient, the sclerotic areas of skin secondary to EMS provided the tissue damage for dystrophic calcification.¹⁴ The mechanism of calcium deposition is poorly understood, but it presents a therapeutic challenge for the physician. The cutaneous mineralization is painful and the tissue affected often ulcerates and fails to heal. Multiple medical therapies have been used including calcium channel blockers and colchicine, but success has been limited. A low calcium diet may be helpful.¹⁴

Osteoporosis is the most common clinical skeletal disorder.¹⁵ Women primarily are affected as bone mass decreases with age. Patients generally do not have any clinical manifestations until there is a fracture, most commonly an asymptomatic vertebral compression fracture. The diagnosis of osteoporosis is made if the patient has low bone mass, microarchitectural disruption of bone, and increased skeletal fragility. In the case of osteoporosis, the bone density of the patient is more than 2.5 SDs below the mean value of young adults of the same sex and race. In clinical practice, microarchitecture of bone is not routinely assessed, because it requires a bone biopsy. Often, low bone mass alone or a history of a nontraumatic fracture with no other explanation confirms the clinical impression of osteoporosis. Laboratory investigations should aim to exclude secondary causes of osteoporosis, which include osteomalacia, hyperthyroidism, hyperparathyroidism, renal

failure, and malignancy. Expert opinion currently recommends that all patients with osteoporosis have blood chemistry, complete blood count, and serum thyrotropin measured¹⁵; all were within reference range in our patient.

Our patient's osteoporosis complicated her treatment plan; the cessation of calcium citrate, alendronate sodium, and raloxifene hydrochloride could result in further bone density loss and subsequent fractures. The literature does not report the development of calcinosis cutis in patients taking alendronate sodium or raloxifene hydrochloride, and a small pilot study conducted by Hill et al¹⁶ found that the rate of coronary arterial calcification was not affected by alendronate sodium.

Robertson et al¹⁷ investigated the use of minocycline as therapy for calcinosis cutis patients with limited cutaneous systemic sclerosis. Eight of 9 patients had a reduction in the frequency of ulceration and inflammation associated with the calcium deposits, and the deposits decreased in size. However, the drug had the unanticipated side effect of making the calcium deposits bluish-black, which may be intolerable for patients.¹⁷ Thus, the only treatment option in many cases is surgical removal of affected areas.

In summary, this case of calcinosis cutis may represent a late sequelae of EMS, which has not been previously documented. This finding presents a therapeutic challenge to the physicians managing patients. Physicians still are trying to determine how these patients are best managed and what workup is required.

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