Dystrophic calcinosis in a patient with overlap syndrome (scleroderma and rheumatoid arthritis) treated by leflunomide

A case report

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Abstract
Rationale: Dystrophic calcinosis occurs in chronically damaged tissue in patients with complicated autoimmune diseases. The therapeutic options are limited, and the treatment response rate is variable. Here, we describe a rare case of dystrophic calcinosis treated with leflunomide in a patient with overlap syndrome.

Patient concerns: A 53-year-old woman who was diagnosed with overlaps syndrome (systemic sclerosis [SSc] with rheumatoid arthritis [RA]), presented to our hospital with pain and swelling in both wrists, and underwent radiography, bone scan, and biopsy examination.

Diagnoses: This patient was diagnosed with dystrophic calcinosis in overlaps syndrome.

Interventions: The conventional disease-modifying drugs were not effective. Hence, leflunomide was administered.

Outcomes: Simple radiography and bone scan showed resolved mass-like dystrophic calcinosis on both wrists of the patient after the use of leflunomide.

Lessons: The control of underlying disease is important in the treatment of dystrophic calcinosis. The use of leflunomide maybe an option in treatment of dystrophic calcinosis combined with RA.

Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism, RA = rheumatoid arthritis, SSc = systemic sclerosis.

Keywords: arthritis rheumatoid, calcinosis, leflunomide, scleroderma systemic

1. Introduction
Dystrophic calcinosis with overlap syndrome is extremely rare in rheumatic diseases. The exact mechanism of calcinosis is still unknown, and no approved effective therapy currently exists. However, in this article, we experienced a rare case of dystrophic calcinosis overlapping with systemic sclerosis (SSc) and rheumatoid arthritis (RA). The patient was treated medically using leflunomide, instead of surgery.

2. Case report
A 53-year-old woman was admitted to our hospital in December of 2013, with complaints of slow growing mass on her hand with no history of trauma. She had been treated for limited cutaneous SSc since 2008. Based on the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria, a diagnosis of SSc was confirmed according to the presence of the following findings: skin thickening of fingers (4 points), Raynaud’s phenomenon (3 points), antinuclear antibody 1:640 (nucleolus type; anticentromere and anti-scl70 antibodies: 3 points). She was on calcium channel blockers, proton pump inhibitors, and colchicine. In 2009, she was diagnosed with RA based on the RA 2010 ACR criteria according to the following findings: multiple arthritis with increased rheumatoid factor at 218U/mL (normal < 18U/mL) and anticitrullinated protein antibody at 538IU/mL (normal < 5 IU/mL). In 2011, we diagnosed her with overlap syndrome including RA and SSc. She was treated with methotrexate, hydroxychloroquine, sulfasalazine, and low-dose steroid. In addition to these clinical signs, she could not move her hands due to pain. Her peripheral blood smear showed the following: leukocyte count, 13,200/mm3; hemoglobin level, 10.3g/dL; and platelet count, 336,000/mm3. Her blood chemistry revealed sodium, 142mM/L; potassium, 3.8mM/L; chloride, 101mM/L; calcium, 7.6 mg/dL; phosphorous, 3.6 mg/dL; uric acid, 8.6 mg/dL; total protein, 6.7 g/dL; albumin, 3.5 g/dL; aspartate aminotransferase, 54 U/L; alanine aminotransferase, 15 U/L; alkaline

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phosphatase, 154U/L; total bilirubin, 1.2mg/dL; prothrombin time, 10.7 seconds; erythrocyte sedimentation rate, 120mm/h (normal < 30mm/h); and C-reactive protein, 9.14mg/dL (normal < 0.05mg/dL). Her urinalysis results were normal. Viral antibody tests were performed again, revealing HBs Ag (-), HBs Ab (-), HCV Ab (-), and Hba1C of 5.4%. Simple radiography of both hands showed tumoral calcinosis. Bone scan showed active arthritis on both hands (Fig. 1). Biopsy and histologic findings were consistent with dystrophic calcinosis and collagen vascular overlap syndrome. Her treatment medication was changed to leflunomide 20mg/d, methotrexate 15mg/wk, and prednisolone 10mg/d. One month after the change in medication, improvement in arthritis was noted in both hands. She was free from hand pain with no changes in the neurological status or recurrence. Twelve months follow-up imaging revealed improved tumoral calcinosis (Fig. 2). Controlled rheumatoid disease activity has been obtained after using leflunomide, until recently.

Written informed consent was obtained from the patient for the purpose of publication of this case report and any accompanying image. A copy of the patient consent form is available for review by the editor of this journal. Because of this, there is no need to conduct special ethic review and the ethical approval is not necessary.

Figure 1. The simple radiography shows calcified nodule and 3-phase bone (Tc-99m DPD scan by ECAM camera, approach by right antecubital vein) scan shows inflammatory change in both wrists (A and B).
3. Discussion

Although dystrophic calcinosis is rare in connective tissue diseases, and the accurate pathogenesis unknown,[1] it is known to occur in tissues that are somehow altered to promote calcification with normal serum levels of calcium and phosphorous as in our present patient. The pathophysiology of dystrophic calcinosis may include chronic tissue inflammation, structural defects, and hypoxemia.[1] Moreover, the calcium and phosphorous can bind to the denatured proteins of the necrotic cells that may act as a core for dystrophic calcinosis in location of trauma or inflammation.[2] In this case, repeated inflammatory chain reactions may play an important role in the development of calcinosis in hands, where synovitis often occurs in patients with refractory collagen vascular diseases, especially in those with RA. Dystrophic calcinosis is often presented as a developing mass in the soft tissues around major joints, such as elbows and knees, and it often has a hard nodule in sacral area that can result in secondary local inflammation, muscle atrophy, or joint contracture. The pleomorphic calcium phosphate crystals are restricted to soft tissue, usually extensor surfaces of joints with bone destruction and the growth of pleomorphic calcium phosphate crystals may also lead to mass effects on the neurovascular structures. However, sometimes calcinosis can remain asymptomatic, with radiographs showing calcific deposits.[3,4] There is

Figure 2. After use of leflunomide, resolved calcified nodule and improved arthritis in both hand (A and B).
no standard treatment for dystrophic calcinosis, although warfarin, colchicine, probenecid, bisphosphonate, diltiazem, minocyline, aluminum hydroxide, and salicylate have been used. However, none of the drugs convincingly prevents or reduces dystrophic calcinosis with great success. Some reports suggested that surgical resection could be beneficial for large lesions and should be considered when dystrophic calcinosis cause severe local pain or diminishes the quality of life. However, in our case, the patient was treated with leflunomide, an immunomodulatory drug hypothesized to affect the pathogenesis of RA by invoking a response from activated T lymphocytes. The primary action of leflunomide was selective inhibition of dihydroorotate dehydrogenase, a key enzyme involved in pyrimidine synthesis, thus inhibiting de novo pyrimidine synthesis. Whether leflunomide had a local direct effect on calcified nodule or a systemic indirect effect on RA inflammation is unknown; however, we hypothesize that the treatment of RA inflammation resolves dystrophic calcinosis. In some reports, the prognosis of dystrophic calcinosis may improve in patients who have undergone an early initiated aggressive therapy for underlying disease. Moreover, in the present case, an early aggressive therapy was initiated from the beginning of RA and the drug change was changed to leflunomide during the course of the disease.

In some respects, the use of leflunomide in our case may have accidentally treated dystrophic calcinosis. However, we inferred that the treatment of the underlying disease was the best clinical management of dystrophic calcinosis, and the use of leflunomide might be a pharmacological treatment option for treating dystrophic calcinosis in RA patients.

**Author contributions**

**Validation:** Sung Won Lee.

**Visualization:** Won Tae Chung.

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**Writing – review & editing:** Sang Yeob Lee.

**References**

[1] Reiter N, El-Shabrawi L, Leinweber B, et al. Calcinosis cutis. Part I: diagnostic pathway. J Am Acad Dermatol 2011;65:1–2.

[2] Boulman N, Stobodin G, Rozenbaum M, et al. Calcinosis in rheumatic diseases. Semin Arthritis Rheum 2005;34:805–12.

[3] Valenzuela A, Chung L. Calcinosis: pathophysiology and management. Curr Opin Rheumatol 2013;27:542–8.

[4] Ak-Najjar M, Jackson MJ. Non-healing leg ulcers in a patient with dystrophic calcification and CREST syndrome: a challenging clinical case. Int Wound J 2011;8:537–41.

[5] Shibuya S, Kawaguchi Y, Arima N, et al. Tumoral calcinosis in bilateral facet joints of the lumbar spine in scleroderma. Case report. J Neurosurg Spine 2006;5:451–4.

[6] Primetis E, Dalakidis A, Papacharalampous X, et al. Extensive tumoral calcinosis in a patient with systemic sclerosis. Am J Orthop 2010;39: E108–10.

[7] Qadri SRM, Choksey MS, Shad A. Tumoural calcinosis of the cervical spine: case report, pathogenesis and differential diagnosis. Br J Neurosurg 2010;19:185–90.

[8] Dutz J. Treatment options for the cutaneous manifestation of systemic sclerosis. Skin Ther Lett 2009;6:3–5.

[9] Kalajian AH, Perryman JH, Callen JP. Intravenous immunoglobulin therapy for dystrophic calcinosis cutis: unreliable in our hands. Arch Dermatol 2009;145:334.

[10] Smack D, Norton SA, Fitzpatrick JE. Proposal for pathogenesis-based classification of tumoral calcinosis. Int J Dermatol 1996;35:265–71.

[11] Rückermann K, Fairbanks LD, Carrey LA, et al. Leflunomide inhibits pyrimidine de novo synthesis in mitogen-stimulated T lymphocytes from healthy humans. J Biol Chem 1996;271:21682–91.

[12] Smolen JS, Tohidast Akrad M, Gal A, et al. The role of T lymphocytes and cytokines in rheumatoid arthritis. Scand J Rheumatol 1996;25:1–4.

[13] King JJ, Brennan KB, Crawford EA, et al. Surgical complications associated with extensive tumoral calcinosis. Am J Orthop 2011;40:247–52.

[14] Smucker JD, Heller JG, Bohman HH, et al. Surgical treatment of destructive calcific lesions of the cervical spine in scleroderma: case series and review of the literature. Spine 2006;31:2002–8.