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Case Report

Systemic sclerosis and calcinosis cutis: response to rituximab

H. Poormoghim* MD, E. Andalib* MD, A. R.Almasi† MD and E. Hadibigi* MD

**Scleroderma Study Group, Department of Rheumatology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, and †Department of Radiology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran*

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SUMMARY

What is known and objective: **Calcinosis cutis (or cutaneous calcification) is a type of calcinosis wherein calcium deposits form in the skin and frequently encountered in limited cutaneous subtype of disease. So far, no treatment has shown an explicit beneficial effect. Medical therapy for calcinosis cutis with rituximab is limited and of variable benefit.**

Case summary: **Our patient was 54-year-old lady, a case of limited cutaneous scleroderma with widespread progressive calcinosis cutis unresponsive to current therapy. She went under treatment with rituximab with no successful outcome.**

What is new and conclusion: **Results of therapy with rituximab on regression/improvement of systemic sclerosis-related calcinosis are limited and non-conclusive.**

INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune disease involving multiple systems. It is characterized by microangiopathy leading to fibrosis of skin and visceral organs. Based on the extent of skin involvement, SSc is classified into two subtypes: diffuse cutaneous sclerosis (dcSSc) and limited cutaneous sclerosis (lcSSc).

Calcinosis is a well-known phenomenon that can occur in 25% of patients with SSc.[1] It is usually subcutaneous and more frequent in the lcSSc subtype. Calcinosis cutis is a disorder in which progressive deposition of insoluble calcium formed in the skin with a normal serum calcium and phosphorous level. When calcinosis is located in small areas of the extremities or joints, it is called circumscripta, and when it involves subcutaneous and fibrous structure of muscles and tendons, calcinosis universalis.

Therapeutic options vary and include low-dose warfarin,[2] intravenous immunoglobulin,[3] bisphosphonates,[4] intralesional corticosteroids,[5] colchicine,[6] minocycline and diltiazem.[7] Recently, two case reports discussed the efficacy of rituximab (RTX) in the improvement of calcinosis.[7,8] Another study reported a flare despite such treatment.[9] There are no standard therapeutic options available, and pharmacological agents and/or alternative therapies have not been effective.[7] In our case, the patient was treated with RTX to alleviate the patients' pain and disability.

Correspondence: H. Poormoghim, Scleroderma Study Group, Department of Rheumatology, Firoozgar Hospital, Behafarin Ave., Tehran, Iran. Tel.: +989123841446; fax: +982182141321; e-mails: h-poormoghim@tums.ac.ir, hadipoormoghim@yahoo.com

CASE REPORT

Herein, we report a 54-year-old Caucasian woman who we first diagnosed with SSc in 1991. The patient had the lcSSc subtype with Raynaud's phenomenon, oesophageal reflux and skin stiffness of face and the extremities distal to elbow and knee Through the first year of diagnosis, she had received low-dose prednisone (5 mg/day), diltiazem (60 mg/day) and omeprazole (20 mg twice daily). In 2006, patient noted well defined, hard plaques over both wrists and right shoulder, which future radiographic evaluation revealed calcinosis. Despite the administration of warfarin 1·25 mg/day for 3 months (after which time she refused continuing), colchicine 1 mg/day and diltiazem 120 mg/day in the follow-up period, we noticed a progressive aggravation in the number and size of the calcinosis lesions. Between 2006 and 2013, she had had 2–3 visits per year and had been admitted twice due to infection at calcinosis sites on right leg and foot. During that period, she was taking calcium blocker and colchicine with no response.

In July 2013, she complained of hip pain and difficulty in hip movement. On physical examination, findings included the limitation of motion of both hips, a modified Rodnan skin score (mRSS) of 16, a right foot ulcer, sclerodactyly, numerous firm yellowish-white subcutaneous lesions on her shoulder, elbows and legs measuring approximately 5–6 cm in diameter. Radiographic examination of her hip showed multiple tumoral calcified soft tissue lesions around joints. She had no symptoms suggestive of heart or lung disease. The forced vital capacity (FVC) and diffusion capacity of carbon monoxide (DLCO) were 75% and 78% of predicted value, respectively. Further radiography of elbows, chest and pelvis revealed multiple calcified lesions prior and after RTX therapy (Figs 1–3).

Some of the skin lesions were soft and fluctuant with an open sinus and chalky white discharge (for about 2 years), and some had no discharge but had resulted in scars. Her blood tests showed a haematocrit of 32·6%, ESR of 57 mm/h and a CRP of 4 mg/L (normal < 5 mg/L), negative rheumatoid factor, strongly positive ANA at a titre of 1 : 640 with a speckled pattern. Anti-TOPO antibodies (Abs) titre by ELISA test was 288 (normal: up to 25 AU/mL). Serum tests showed a calcium of 7·9 (8·6–10·6 mg/dL), phosphorus 3 (2·5–5 mg/dL), alkaline phosphatase 219 (up to 270 iu/L), magnesium 2·1 (1·6–3 mg/dL), 25-hydroxyvitamin D 45 ng/dL (30–70 ng/mL), parathormone (PTH) 70 (15–68·5 pg/dL).

In October 2013, with the diagnosis of extensive calcinosis cutis unresponsive to all administered therapies and given the debilitating status of the patient, we obtained a signed informed consent to treat her with RTX (two infusions at 2-week intervals, 1 g each

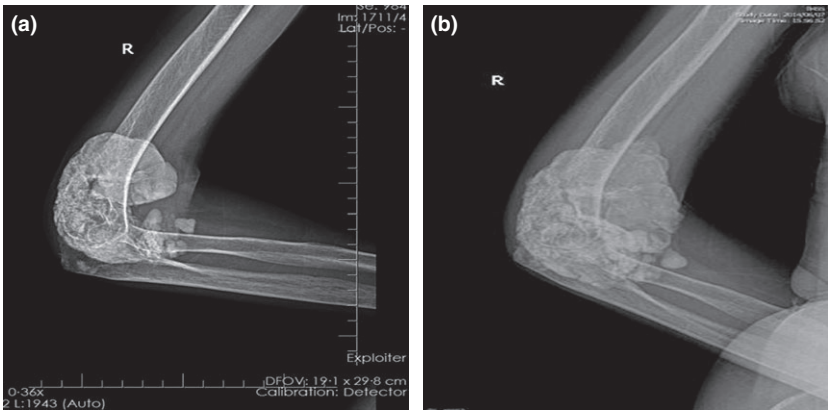

Fig. 1. Multiple large calcifications on right elbow: (a) prior to treatment with Rituximab (2013) and (b) After treatment with Rituximab (2014).

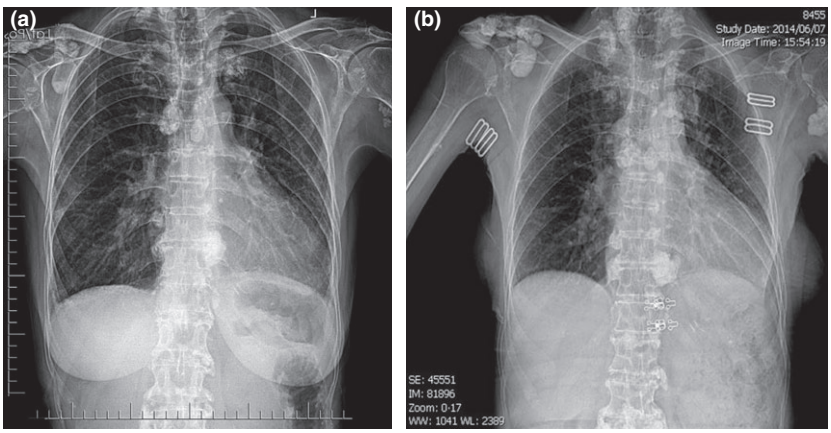

Fig. 2. Multiple large calcifications of right shouder on chest X-ray: (a) prior to treatment with Rituximab (2013) and (b) after treatment with Rituximab (2014).

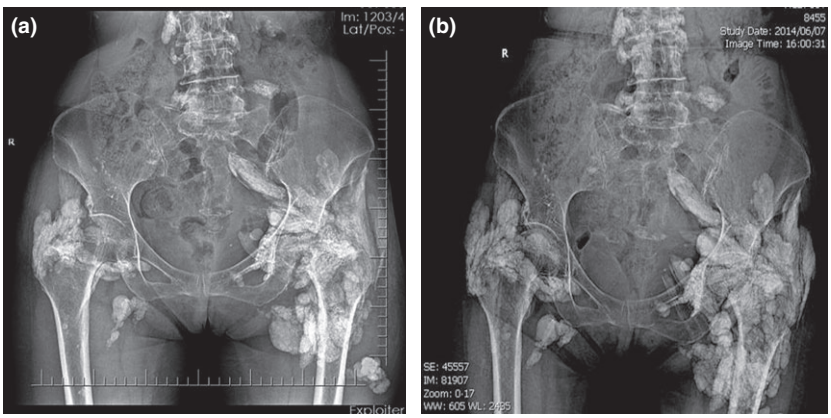

Fig. 3. Multiple large calcifications on pelvic X-ray: (a) prior to treatment with Rituximab (2013) and (b) after treatment with Rituximab (2014).

and 1 gr 6 months later). Post-RTX evaluation at 9 months showed a significant alleviation of hip pain that required lower dose of analgesics. Radiographic evaluation revealed increased number/sizes of calcified lesion; additionally, she complained about growing mass in groin and right shoulder. Further radiography of elbows, chest and pelvis revealed multiple calcified lesions prior and after RTX therapy (Figs 1–3).

At this time, total mRSS was 14 with no change in pulmonary function (FVC and DLCO were 72% and 80%, respectively). Ten months after starting RTX, the patient admitted with aspiration

pneumonia and multiple digital ulcer infection. Despite the rigorous antibiotic therapy, patients could not survive.

DISCUSSION

We reported a case of lcSSc with calcinosis cutis and anti-Topo-positive Abs. Although positive anti-Topo Abs are reported mainly in the diffuse subtype of SSc, our case was classified as lcSSc based on skin fibrosis extension.[10]

Our decision to use RTX was based on the patient's unresponsiveness to current therapies and several recent reports on its clinical efficacy on SSC-associated calcinosis.

A beneficial effect on calcinosis of 4 weekly infusions of RTX (375 mg/m^2) with repeated dose in 6 months in a 53-year-old woman with lcSSc was reported, showing an improvement in the size and number of calcifications within 12 months.[7]

de Paula *et al.*[8] published a case of a 54-year-old female with lcSSc who was taking RTX for interstitial lung disease and arthritis, and she showed an improvement in calcinosis. This report demonstrated a clinical and radiographic improvement of calcinosis following 7 months of RTX therapy.

Interestingly, a flare of calcinosis in a 61-year-old woman with dcSSc who underwent two RTX infusions in a 2-week interval (1 g each) followed by 1 g RTX infusion every 6 months was reported by Hurabielle *et al.*[9]

Our case was similar to the case presented by Hurabielle *et al.*[9], with multiple tumoral calcified lesions, positive anti-TOPO antibodies and failure to respond to therapy.

The mechanism of soft tissue calcification in SSc is not fully understood. Involvements of the microenvironment and trauma have been considered as implicated factors. This makes it difficult to identify a treatment target. As a result, there are no standard therapeutic approaches in the treatment for calcinosis in SSc.

There is some hypothesis for a beneficial effect of diltiazem through the inhibition of calcium influx in affected tissues and of minocycline, by its calcium-binding properties.[7]

The mechanism of action of RTX is mediated by B-cell depletion and its consequences, although the implication of B cells in the formation of calcinosis is not known; neither is a RTX action on calcinosis known. Several factors could affect the response to therapy such as vasculopathy, severity of ischaemia and microtrauma.[4] However, severity of calcinosis, type of autoantibodies and differences in treatment protocol may also play a role in response to therapy.

WHAT IS NEW AND CONCLUSION

We presented a case of lcSSc with progressive calcinosis cutis, positive anti-TOPO Abs with no response to RTX therapy. Efficacy of treatment with RTX in SSc-associated calcinosis is shown to be inconsistent. Therefore, decisions for RTX use should be individualized based on clinical judgement. We believe that future controlled trials on calcinosis could shed light on a possible different dosage of RTX in this situation.

FUNDING

None.

CONFLICT OF INTEREST STATEMENT

No conflict of interests to be declared.

REFERENCES

1. Boulman N, Slobodin G, Rozenbaum M, Rosner I. Calcinosis in rheumatic diseases. *Semin Arthritis Rheum*, 2005;**34**:805–812.
2. Yoshida S, Torikai K. The effects of warfarin on calcinosis in a patient with systemic sclerosis. *J Rheumatol*, 1993;**20**:1233–1235.
3. Asano Y, Ihn H, Asashima N *et al.* A case of diffuse scleroderma successfully treated with highdose intravenous immune globulin infusion. *Rheumatology*, 2005;**44**:824–826.
4. Fujii N, Hamano T, Isaka Y, Ito T, Imai E. Risedronate: a possible treatment for extraosseous calcification. *Clin Calcium*, 2005;**1S**:75–78.
5. Al-Mayouf SM, Alsonbul A, Alismail K. Localized calcinosis in juvenile dermatomyositis: successful treatment with intralesional corticosteroids injection. *Int J Rheum Dis*, 2010;**13**:e26–e28.
6. Fuchs D, Fruchter L, Fishel B, Holtzman M, Yaron M. Colchicine suppression of local inflammation due to calcinosis in dermatomyositis and progressive systemic sclerosis. *Clin Rheumatol*, 1986;**5**:527–530.
7. Daoussis D, Antonopoulos I, Liossis SN, Yiannopoulos G, Andonopoulos AP. A case report of Rituximab-induced regression of CREST-related Calcinosis and review of the literature. *Semin Arthritis Rheum*, 2012;**41**:822–829.
8. de Paula DR, Klem FB, Lorencetti PG, Muller C, Azevedo VF. Rituximab-induced regression of CREST-related calcinosis. *Clin Rheumatol*, 2013;**32**:281–283.
9. Hurabielle C, Allanore Y, Kahan A, Avouac J. Flare of calcinosis despite rituximab therapy. *Semin Arthritis Rheum*, 2014;**44**:e5–e6.
10. LeRoy EC, Black C, Fleischmajer R, *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*, 1988;**15**:202–205.