CASE REPORT

Is rituximab an effective treatment of refractory calcinosis?

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SUMMARY

Calcinosis, the deposition of calcified material in soft tissues, is frequently seen in systemic sclerosis and dermatomyositis. Treatment options are limited, with disappointing results. Some recent case reports suggest that rituximab may be an attractive therapeutic option. In case 1, a 54-year-old woman who presented with rheumatoid arthritis in association with scleromyositis was treated with rituximab for rheumatoid arthritis. Despite this, she developed multiple progressive calcinosis, necessitating extracorporeal shock wave lithotripsy to limit calcinosis extension and pain. In case 2, a 38-year-old man, previously treated for an anti-Pm/Scl-positive polymyositis/scleroderma overlap syndrome, presented with multiple tumoural periarticular calcinosis, which progressed despite bisphosphonates, sodium thiosulfate and thalidomide. We decided to start rituximab. Progression of calcinosis was still evident 6 and 12 months after anti-CD20 treatment. Many treatments have been tried to treat calcinosis without demonstrated effectiveness. Presently, rituximab cannot be recommended for this indication in the absence of successful controlled trials.

We present two further cases in which RTX failed to prevent calcinosis progression.

CASE PRESENTATION

A 54-year-old woman presented with rheumatoid arthritis (RA) in association with scleromyositis. Beginning in 2000, she had been treated with methotrexate and adalimumab for RA; both were stopped in 2004 because of hepatic toxicity. In 2005, she was diagnosed with anti-Pm/Scl-positive-polymyositis with interstitial pulmonary fibrosis and weakness of the respiratory muscles. Treatment with corticosteroids was started. In 2006, she relapsed and treatment with methotrexate was begun. Then, 6 months later, azathioprine was started for the persistence of inflammatory arthritis. Despite this treatment, she continued to suffer from arthritis, motivating the replacement of azathioprine by RTX (1 g D1, D15) in March 2007. Anti-CD20 treatment was continued every year. In January 2010, extensive multiple subcutaneous pulpar calcinosis appeared, especially in the right thumb, complicated with a digital ulcer in November 2010. Local treatment by lithotripsy was started. Calcinosis was still evolutive and progressing in 2015.

A 38-year-old man, treated for DM with corticosteroids and methotrexate from 2000 to 2005, showed a rapidly progressive calcinosis in the left wrist in 2006. The evolution was marked by extensive, widespread calcinosis of the right wrist, left elbow and left forearm (figure 2). Alendronate was started in October 2007. After initial clinical and radiological improvements, the calcinosis progressed, and bisphosphonates were discontinued in 2009. In January 2011, the patient presented with new calcifications in the right hand, with complete blockade of the radiocarpal joint. Intravenous pamidronate was ineffective. Sodium thiosulfate was interrupted because of a severe allergic reaction (acute generalised exanthematous pustulosis). In November 2011, thalidomide was started, allowing radiological stability, but after 1 year, the development of an axonal neuropathy led to the discontinuation of thalidomide. In March 2013, RTX (375 mg/m² week 1–4) was initiated for the progression of calcinosis. Calcinosis was progressing at 6 and 12 months.

TREATMENT

RTX is considered as a promising treatment in systemic sclerosis (SSc); indeed, B cells regulated both inflammatory and fibrotic alterations in SSc-related manifestations. During the past years, preliminary

BACKGROUND

Calcinosis is characterised by the deposition of insoluble calcium salts in the skin and subcutaneous tissue.^{1 2} It is associated with various connective tissue diseases; indeed, calcinosis is frequently associated with dermatomyositis (DM; up to 40–70% of the juvenile form) or limited systemic sclerosis (25–40%).¹ Calcinosis is also rarely reported in systemic lupus erythematosus, mixed connective tissue disease and Sjögren's syndrome.¹

Patients with calcinosis can be asymptomatic or suffer from complications, such as large and extensive widespread calcium deposits (especially in juvenile DM), ulcerations, periarticular involvement and pain, all responsible for disability and impaired quality of life.³

No standard treatment for calcinosis has been established. On the basis of previous case reports, small retrospective case series or limited controlled studies, warfarin, diltiazem, minocycline, bisphosphonate, colchicine, intravenous immunoglobulins, sodium thiosulfate and thalidomide have been used to control calcinosis progression, but until now no treatment has shown an unequivocally beneficial effect.^{4 5} While two recent case reports suggested the efficacy of rituximab (RTX) for calcinosis treatment, one still showed a calcinosis flare despite this anti-CD20 therapy.^{6–8}

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Figure 1 Persistent finger calcinosis despite annual treatment with rituximab and lithotripsy.

clinical trials have suggested the therapeutical usefulness of RTX also in refractory cases of SSc, especially with progressive lung and skin involvements; moreover, several case reports provide reasonable evidence of RTX efficiency for SSc-calcinosis.^{6 7 9}

In case 1, RTX was started in March 2007 because of insufficient control of the RA, with a conventional dosage (1 g days 1 and 15). Since then, the patient received RTX once per year. Despite this treatment, new calcinosis sprang up from time to time; we also observed a progression of the disabling subcutaneous pulpar calcinosis, despite repeated lithotripsy treatment (figure 1).

In case 2, in March 2013, RTX was initiated for the progression of calcinosis with an infusion protocol (375 mg/m² weeks 1–4), similar to the two cases reporting his efficiency in calcinosis.^{6 7} Twelve months later, the patient presented a new flare of calcinosis with new locations in the back, right hand and left thumb (figure 2).

OUTCOME AND FOLLOW-UP

In both cases, we observed a progression of calcinosis despite anti-CD20 treatment.

DISCUSSION

Calcinosis is responsible for chronic pain and local inflammation.³ Pain, functional impairment and deterioration in quality of life are the major reasons for calcinosis treatment, with varying degrees of benefits. Many calcinosis treatments have been investigated in case reports or small series, but until now no therapy has proven to be definitively efficacious. No treatment is presently accepted as the ‘standard’ therapy because of the lack of randomised controlled trials.

RTX is an anti-CD20 monoclonal antibody. It induces B-cell depletion and was assessed in the treatment of systemic sclerosis-related refractory interstitial lung disease and skin involvement.¹⁰ It has also been reported to be effective in treating myositis and skin involvement in DM.¹¹ Some case reports suggested the efficacy of RTX for calcinosis treatment, while others showed no improvement of calcinosis (table 1).

Daoussis *et al*⁶ reported the case of a 53-year-old woman with a limited form of systemic sclerosis (calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, telangiectasia (CREST) syndrome) who presented with extensive calcinosis, causing reduced quality of life. She was treated with 375 mg/m² RTX infusions for 4 weeks for interstitial lung disease. At 1 year, the calcifications had diminished, and the pain had disappeared. A second case, reported by de Paula *et al*⁷, was of a 54-year-old woman with limited systemic sclerosis treated with RTX (4 weekly infusions of 375 mg/m²) for interstitial disease and arthritis. They reported complete remission of the calcinosis 7 months after the first infusion. An as yet unpublished study by Narváez *et al*,¹² presented at the American College of Rheumatology in 2014, reported 30 patients with limited or diffuse SSc or overlap syndrome treated by RTX. RTX was effective in 40% of patients with calcinosis (n=11). Giuggioli *et al* reported a series of 10 patients with SSc (diffuse forms n=5) treated by RTX for lung fibrosis, cutaneous or articular manifestations. Of the six patients who had calcinosis, three showed an improvement (1).⁹

In our cases, RTX was not effective; indeed, we observed the progression of calcinosis in both cases of DM and systemic sclerosis. Similarly, Hurabielle *et al*⁸ reported the case of a 61-year-old woman with diffuse systemic sclerosis in which RTX failed to help her calcinosis. Another study evaluating the efficacy of RTX for juvenile DM showed no improvement of

Figure 2 Widespread calcinosis after 1 year of rituximab. Calcification before (A, right part) and after (A left part, B) rituximab treatment.

Table 1 Studies assessing the efficacy of rituximab in the treatment of calcinosis

Reference	Type of study	Patients	Diagnosis	Scheme	Efficacy
6	Case report	Woman, 53 years old	Limited ScS (CREST)	375 mg/m ² , 4 weekly	Yes
7	Case report	Woman, 54 years old	Limited ScS	375 mg/m ² , 4 weekly	Yes
8	Case report	Woman, 61 years old	Diffuse ScS	1 g D1-D15 then 1 g/6 months	No
9	Retrospective study	N=10, 6 with calcinosis	Limited or diffuse ScS	375 mg/m ² , 4 weekly	Yes (50%)
11	Prospective study	N=6	Juvenile DM	ND	No
12	Retrospective study	N=30, 37% with calcinosis	Limited and diffuse ScS, overlap syndrome	ND	Yes (40%)
13	Case report	Man, 35 years old	DM anti-MDA-5	1 g D1-D15	No

CREST, calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasia; D1-D15, day 1 and day 15; DM, dermatomyositis; ND, not done; ScS, systemic sclerosis.

calcinosis in six affected patients.¹¹ Girard *et al*¹³ also reported the case of a 35-year-old man with anti-melanoma differentiation-associated protein 5 DM in which RTX failed to treat calcinosis.

It seems that RTX could be effective in 30–50% of calcinosis related to pure forms of ScS, either in limited or diffuse forms. These two cases pointed out that RTX seems to be ineffective in calcinosis complicating overlapping syndrome or scleromyositis. The complex pathophysiology of each disease could explain these discrepancies.

Learning points

- Calcinosis is a painful and debilitating complication of connective tissue diseases, such as systemic sclerosis and dermatomyositis.
- Two recent case reports suggested that rituximab may be an attractive therapeutic option for the treatment of calcinosis.
- However, we presently demonstrated that rituximab could not be recommended for the treatment of calcinosis in patients with overlapping syndrome or scleromyositis.
- Controlled studies are needed to further evaluate the efficacy of rituximab for this indication.

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Patient consent Obtained.

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