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Case Report

Cancellous bone-like tissue replacement from calcinosis in patients with systemic sclerosis with multiple external root resorption

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ABSTRACT

Calcinosis is frequently observed in patients with systemic sclerosis (SSc). The fundamental treatment of calcinosis has not yet been established. During follow-up, calcinosis in the subcutaneous surface is often spontaneously extracted or remains confined by fibrous tissues. We previously identified a new symptom in SSc patients, multiple external root resorption (MERR), and these patients had calcifications in the nasal spine. Here, we report for the first time that calcinosis at the nasal spine in patients with MERR can be replaced by cancellous bone-like tissue. Patients 1 and 2 were a 62-year-old Japanese female and a 45-year-old Japanese female (respectively) with MERR who had been previously treated for SSc (Patient 1: limited type, positive for anti-centromere antibody; Patient 2: diffuse type, positive for anti-Scl70 and anti-SS-A antibodies). Patient 3 was a 57-year-old female with MERR who had been previously treated for SSc (diffuse type, positive anti-Scl-70 antibody) and underwent denosumab injection for osteoporosis. Cone-beam computed tomography (CBCT) and CT images in the calcifications at the nasal spine in Patient 1 and 2 were replaced with cancellous bone-like tissue, but not in Patient 3. Serum laboratory examination was performed to assess the systemic bone disease. All three patients had normal clinical data within the references, apart from slightly higher 1,25-dihydroxyvitamin D levels in Patient 1. SSc patients with calcinosis in the maxillofacial area need to be examined carefully for bone replacement using CBCT or CT.

1. Introduction

Systemic sclerosis (SSc) is an autoimmune collagen disease characterized by skin fibrosis, angiopathy, and immune disorders. The definitive pathology has not yet been elucidated, and the mortality rate remains high among collagen diseases (Denton and Khanna, 2017). We previously found that patients with SSc have multiple external root resorption (MERR) and exhibit similarity in symptoms in the maxillofacial region (Matsuda et al., 2018; Memida et al., 2019). As a part of the SSc family, CREST syndrome is classified as a limited form characterized by calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia(Velayos, 1979). Calcinosis at the anterior nasal spine is found in patients with MERR (Matsuda et al., 2018; Memida et al., 2019).

Calcinosis is a form of ectopic calcification and biomineralization in which the main mineral component is predominantly hydroxyapatite and is covered by a cell-free connective tissue matrix (Burgess et al., 2021). No definitive treatment method for calcinosis has been

Abbreviations: SSc, systemic sclerosis; MERR, multiple external root resorption; CBCT, cone-beam computed tomography; NSAID, non-steroidal anti-inflammatory drugs; HO, heterotopic ossification; FOP, fibrodysplasia ossificans progressive; POH, progressive osseous heteroplasia; PTH, parathyroid hormone; BAP, bone alkaline phosphatase; RANK, receptor activator of nuclear factor-kappa B; CREST, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.

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established. It is usually not absorbed naturally. It may be spontaneously excreted from subcutaneous connective tissue, especially small deposits. Antibiotics and non-steroidal inflammatory drugs (NSAIDs) are used to prevent inflammation and infection (Valenzuela et al., 2018). Surgical removal is also performed when calcinosis causes neuropathy (Traineau et al., 2020).

Heterotopic ossification (HO) can be hereditary and classified as either fibrodysplasia ossificans progressiva (FOP) (Martelli and Santos, 2014; Nakajima and Ikeya, 2019)or progressive osseous heteroplasia (POH) (Adegbite et al., 2008; Pignolo et al., 2015). Non-hereditary HO is acquired through trauma, including soft tissue injury, trauma or surgery, central nervous system and spinal cord injury, burns, and amputation (Brady et al., 2018; Kent et al., 2018; Moore et al., 2016; Potter et al., 2007; Tippets et al., 2014; Zhu et al., 2015). HO has been reported in a few cases of SSc, but it is unknown how it is generated (Botzoris et al., 2009; Weerakoon et al., 2011).

Computed Tomography (CT) is an important imaging modality for the diagnosis of soft and hard tissue lesions. Cone-beam CT (CBCT) is an important imaging modality for the diagnosis of hard tissue. The advantage of CT compared with CBCT are the firster scanning time, wider field of view, and quantitative evaluation of gray scale with the lesion density (Hounsfield Unit). Conversely, the advantages of CBCT are higher special resolution images, lower installation cost, and the smaller apparatus. (Chindasombatjaroen et al., 2011a, 2011b).

In the present report, we show the remodeling of calcifications into bone-like tissue at the anterior nasal spine in patients with MERR identified via CT and CBCT images.

2. Case reports

This report complies with the Helsinki Declaration, and written informed consent was obtained from all the patients.

Three patients were diagnosed with SSc, and all had MERR (Matsuda et al., 2018; Memida et al., 2019). The patient characteristics and the drugs taken by these patients are described in Tables 1 and 2, respectively.

Patient 1 was a 62-year-old Japanese female patient referred from a local dental office following a tooth fracture. She had previously been treated for SSc (limited type, positive for anti-centromere antibody), Sjögren's syndrome, autoimmune hepatitis, reflux esophagitis, interstitial lung disease, calcinosis, Raynaud's phenomenon, and hypertension.

Patient 2 was a 45-year-old Japanese female patient referred from a local dental office for examination and treatment of tooth resorption. She had been previously treated for SSc (diffuse type, positive anti-Scl70, anti-SS-A antibody), Raynaud's phenomenon, digital ulcers, and interstitial lung disease.

Patient 3 was a 57-year-old Japanese female patient referred from the Department of Rheumatology at a local hospital. She had been previously treated for SSc (diffuse type, positive anti-Scl70 antibody), Raynaud's phenomenon, digital ulcers, dry mouth (not diagnosed with Sjögren's syndrome), iron deficiency anemia and osteoporosis. After she suffered a left femur fracture, she was diagnosed with osteoporosis and had been taking denosumab since September 2018.

Table 1
Characteristics of patients.

	Patient 1	Patient 2	Patient 3
Age (years)	62	45	57
Body mass index (kg/m^2)	16.7	19.1	15.6
antibody	centromere	Scl70 SSA	Scl70
Classification	Lc SSc	Dc SSc	Dc SSc
mRSS	27	13	29
Raynaud's phenomenon	+	+	+
Calcinosis	+	−	−
Digital ulcers	−	+	+
Reflux esophagitis	+	−	−
Interstitial lung disease	+	+	−
Sjögren's syndrome	+	−	−
Other diseases	Hypertension		Iron deficiency anemia, osteoporosis

Lc, limited type; Dc, diffuse type; SSc, systemic sclerosis; mRSS, modified Rodnan skin score.

Table 2
Medications for each patient.

	Drugs
Patient 1	Angiotensin II receptor blocker
	Ca-channel blocker
	Aminoleban (branched-chain amino acid-enriched nutrient)
	Vonoprazan fumarate (potassium-competitive acid blocker)
	Polaprezinc (zinc-L-carnosine)
	Sodium alginate
	Aluminum hydroxide gel
	Magnesium hydroxide
	Mosapride citrate hydrate
	Bosentan hydrate (endothelin receptor antagonist)
Patient 2	Tocopherol nicotinate
	Bosentan hydrate
Patient 3	Pilocarpine hydrochloride (muscarinic acetylcholine receptor agonist)
	Sarpogrelate hydrochloride (5HT2A receptor antagonist)
	Beraprost Sodium (agonist for prostacyclin receptor)
	Bosentan Hydrate
	Vonoprazan fumarate (potassium-competitive acid blocker)
	Sodium ferrous citrate
	Denosumab (antibody against RANKL, subcutaneously injection)

2.1. Cone-beam computed tomography and computed tomography

Ectopic calcifications at the nasal spine were evaluated using cone-beam computed tomography (CBCT) and computed tomography (CT) analysis. CBCT in Patient 1 showed calcification on the left and right sides of the nasal spine in May 2017 (Fig. 1A–B). However, in 2021, cancellous bone-like tissue formation was observed on the left side (Fig. 1C–D). Density of the lesions (in Hounsfield units, HU) of calcification at the nasal spine in June 2016 (Fig. 2A–B) and in 2021 (Fig. 2D–E) were evaluated: the HU of the calcification on the left side of the nasal spine in 2016 was significantly lower than that in 2021 (Fig. 2C, F, and Table 3). A part of the calcification at the nasal spine of Patient 2 on the CBCT image in 2018 (Fig. 3A–B) was reformed to bone-like tissue in 2021 (Fig. 3C–D), although the calcification at the nasal spine of Patient 3 in 2018 (Fig. 4A–B) did not reform to bone-like tissue in 2021 (Fig. 4C–D).Calcification sizes are shown at Table 4.

2.2. Laboratory examination

Intact parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (vitamin D), calcium, phosphorus, and bone alkaline phosphatase (BAP) in the serum levels of Patients 1 and 2 were evaluated to assess systemic bone disease (Vammi et al., 2021). Vitamin D levels were slightly higher than the Japanese reference in Patient 1. Other biomarkers were within normal ranges in both patients (Table 5).

3. Discussion

Here, we have reported two SSc patients with MERR who showed replacement of calcification by cancellous bone-like tissue in the nasal spine, even though these patients had no systemic bone abnormalities (Patient 1 and Patient 2).

We have previously found calcification in the nasal spine of patients with SSc and MERR(Memida et al., 2019). There are several reports of calcification in the facial region, such as in the lower jaw and

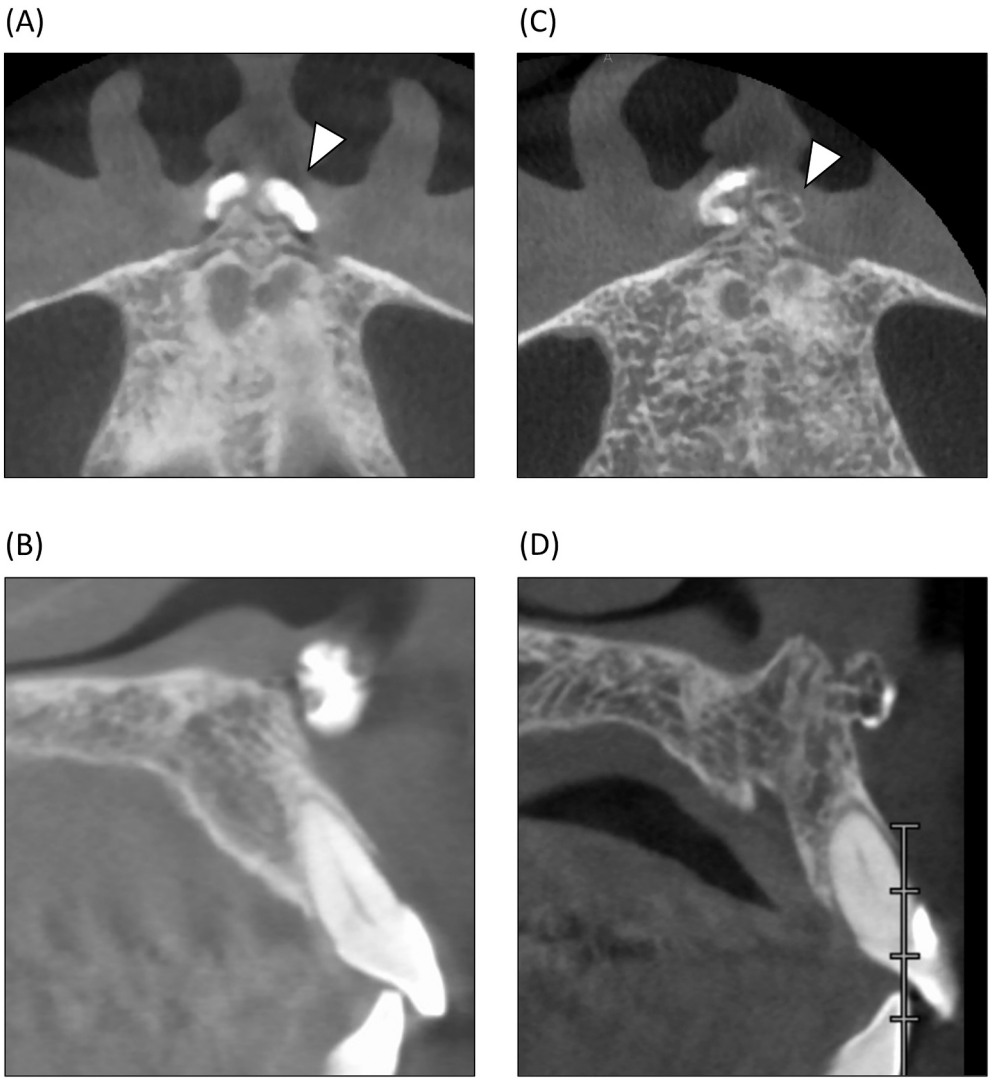

Fig. 1. CBCT images at nasal spine in Patient 1.
Calcification was evaluated by CBCT in Patient 1 in May 2017 (A, B) and April 2021 (C, D). White arrowheads show cancellous bone-like tissue replacement from calcification on the left side. CBCT, cone-beam computed tomography.

temporomandibular joint (Chikazu et al., 2008; Nestal-Zibo et al., 2009). The calcification was removed, and histopathological analysis revealed dystrophic calcification confined by collagen fibers (Chikazu et al., 2008). It has been reported that the collagen necessary for forming dystrophic calcification is synthesized by myofibroblasts (Simionescu et al., 2007). Since the definitive mechanism of calcinosis is unknown, a fundamental treatment has not been established. Although surgical removal can be an effective treatment, the surgical burden on the patient is heavy. Therefore, follow-up in cases where patients have no symptoms has been performed with NSAIDs or antibiotics (Valenzuela and Chung, 2015a, 2015b). We previously reported that surgical resection of subcutaneous calcinosis of the knee was performed due to pain, and we found that it was a heterotrophic calcification (Matsuda et al., 2018). However, in the present report, none of the patients had symptoms around the maxillofacial region; therefore, follow-up was performed. Clinical reports have shown that Ca2+ channel blockers are effective in treating calcinosis (Valenzuela and Chung, 2015a, 2015b). Patient 1 was taking a Ca^{2+} channel blocker for hypertension, but with no effect on the calcinosis. The course of subcutaneous calcinosis without treatment or extraction is longer with further deposition of mineralized tissue such as hydroxyapatite in diseased tissue, but we first found that calcification was replaced with bone-like tissue. Changes in calcinosis are easily detected on CT images, which are also effective for observing morphological changes (Freire et al., 2013). Bone replacement from calcinosis and the status of the replaced bone (i.e., if it is hypertrophic or resolved) must be monitored periodically by CBCT since bone tissue hypertrophy or calcinosis can cause breathing problems. Additionally, this is the first description of systemic calcinosis evolving into bone. Although first observed in the maxillofacial region in this case report, it is necessary to investigate whether ectopic ossification results from systemic calcinosis, especially in areas close to the bone. Bone addition in the maxillofacial region occurs at the mandibular and palatine torus and through oral exostoses, which are localized growths formed by dense cortical bone with limited trabecular bone involvement (Morrison and Tamimi, 2013; Seah, 1995). However, in these cases, at the site where calcinosis was observed, the calcinosis disappeared and was replaced with cancellous bone-like tissue.

Although there have been reports of HO in many tissues (Lees-Shepard and Goldhamer, 2018), there have been no reports of calcification being replaced by HO. Acquired musculoskeletal trauma-induced HO and neurogenic trauma-induced HO are caused by a mixture of intrachondral and intramembranous ossification (Kazezian and Bull, 2021). Non-traumatic HO was found on the wrists of dialysis patients, with elevated blood levels of PTH and BAP, and frequent wrist movements

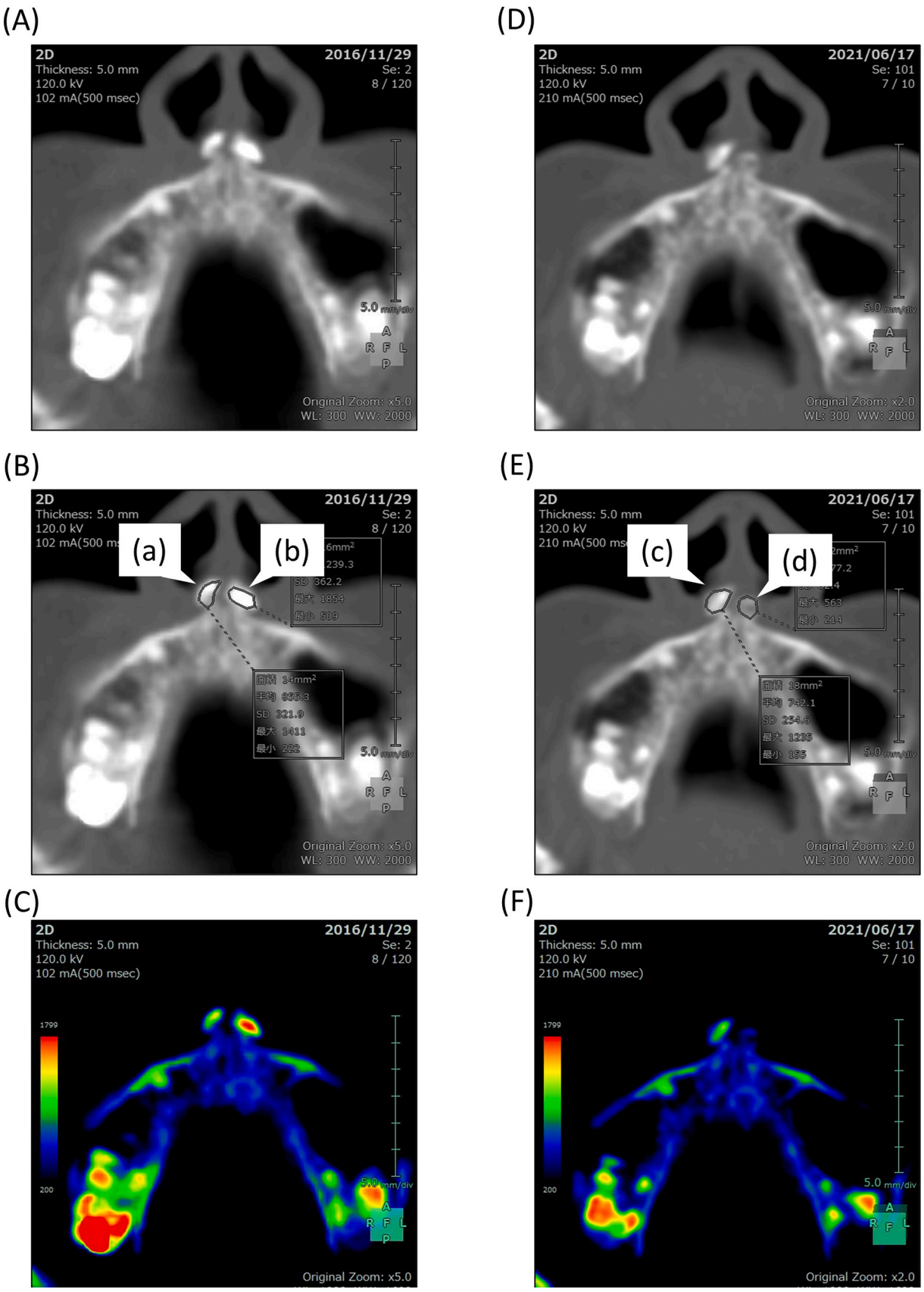

Fig. 2. CT images and the density of the lesion (HU units) analysis at nasal spine in Patient 1
Calcification was evaluated by CT in Patient 1 in November 2016 (A, B, C) and June 2021 (D, E, F). HU units of calcification or bone-like tissue in the nasal spine in 2016 (B (a), (b)) and 2021 (E (c), (d)) were assessed. Color maps based on HU units are shown in November 2016 (C) and June 2021 (F). CT, computed tomography.

Table 3
The density of the lesion (in HU units) in calcification in nasal spine.

		The density of the lesion (HU)		
		Mean ± SD	Max	Min
Right side in nasal spine	11/29/2016 (a)	855 ± 321	1411	222
	06/17/2021 (c)	742 ± 255	1235	155
Left side in nasal spine	11/29/2016 (b)	1239 ± 362	1854	509
	06/17/2021 (d)	377 ± 82	563	214

HU, Hounsfield unit; SD, standard deviation.

have been reported to induce microtrauma to calcification and bone formation (Hatano et al., 2021). In our cases of bone replacement of calcinosis, the concentrations of bone-related factors, calcium, and phosphorus in the blood were within the normal range. In addition, these patients did not experience trauma to the anterior nasal spine nor is it a place where a continuous load is applied. Therefore, it is unknown how these calcifications were generated in the anterior nasal spine and replaced by bone. Induced osteoclasts are considered to cause phagocytosis and bone remodeling by differentiated osteoblasts in HO (Jin et al., 2021; Matsuo and Irie, 2008)However, the mechanisms underlying bone replacement need to be investigated.

In Patient 3, although calcification was observed in the anterior nasal spine, bone-like tissue replacement was not observed. Bisphosphonates, which lead to osteoclast apoptosis (Drake et al., 2008), have been reported to be effective against calcinosis (Mori et al., 2012; Traineau et al., 2020), FOP, and HO (Aubut et al., 2011; Yolcu et al., 2020), although there is no consensus on their effectiveness. Patient 3 was clinically injected with denosumab (an inhibitor of receptor activator of nuclear factor-kappa B [RANK] ligand), which prevents the activation of RANK on the surface of osteoclasts and osteoclast precursors, ultimately inhibiting osteoclast formation preparation for osteoporosis (Castellano et al., 2011). Although there is no report mentioning the use of denosumab to treat calcinosis or HO, hypertrophy of the calcification and a lack of bone replacement may have occurred in Patient 3 because denosumab targets osteoclast inactivation similar to bisphosphonate. Bisphosphonates or denosumab may be potent in the treatment of bone replacement from calcinosis found in patients with SSc.

The present case reports have several limitations. First, the lack of bone-like tissue biopsy. To identify the tissue as bone tissue, a histopathological analysis is needed. Second, only three cases were included. An investigation on the relationship between bone-like tissue formation and calcinosis in SSc patients requires a cohort study. Third, since CBCT is difficult to quantify using HU, quantifying the calcifications in patients 2 and 3 was also difficult as well. However, since it is possible to show density differences on CT images, we could show the change in

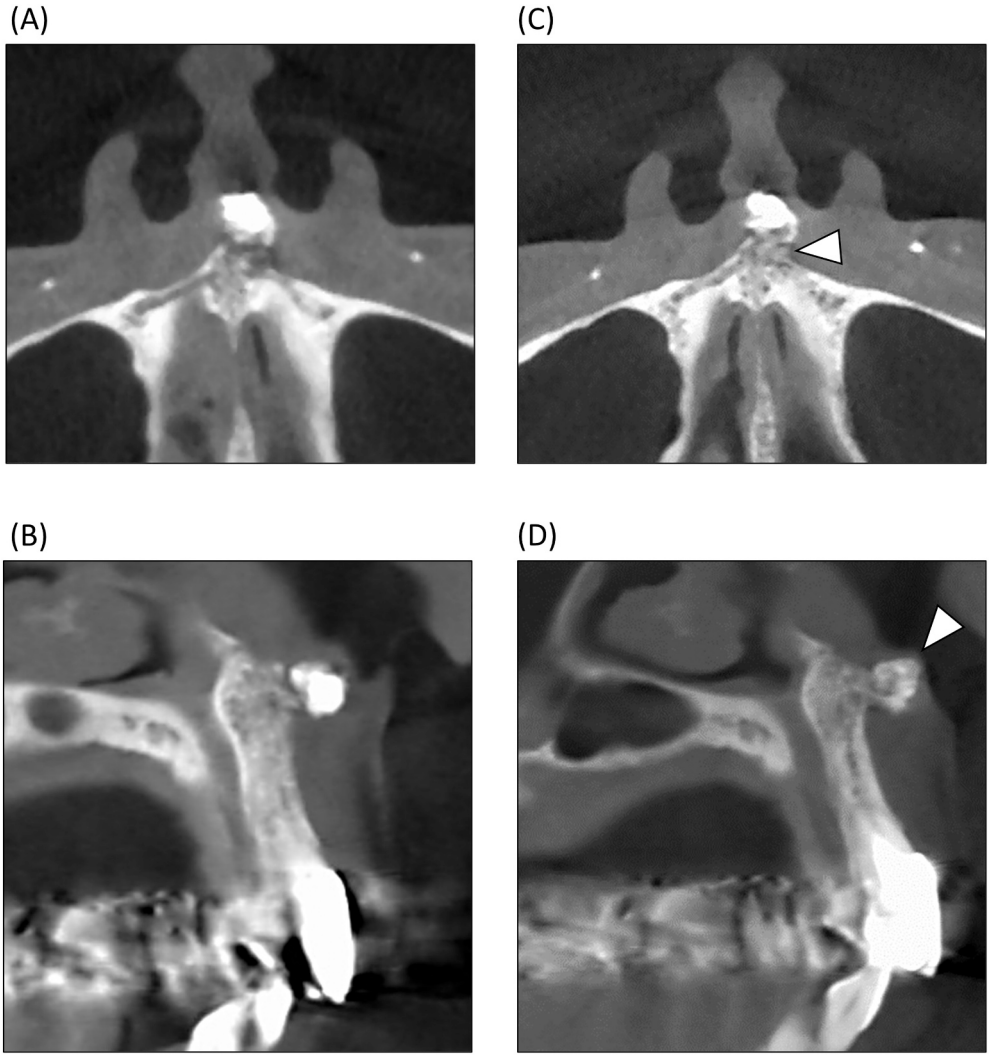

Fig. 3. CBCT images at nasal spine in Patient 2.
Calcifications were evaluated by CBCT in Patient 2 in August 2018 (A, B) and June 2021 (C, D). Bone-like tissue formation in a part of the calcification is observed (white arrowhead; C, D). CBCT, cone-beam computed tomography.

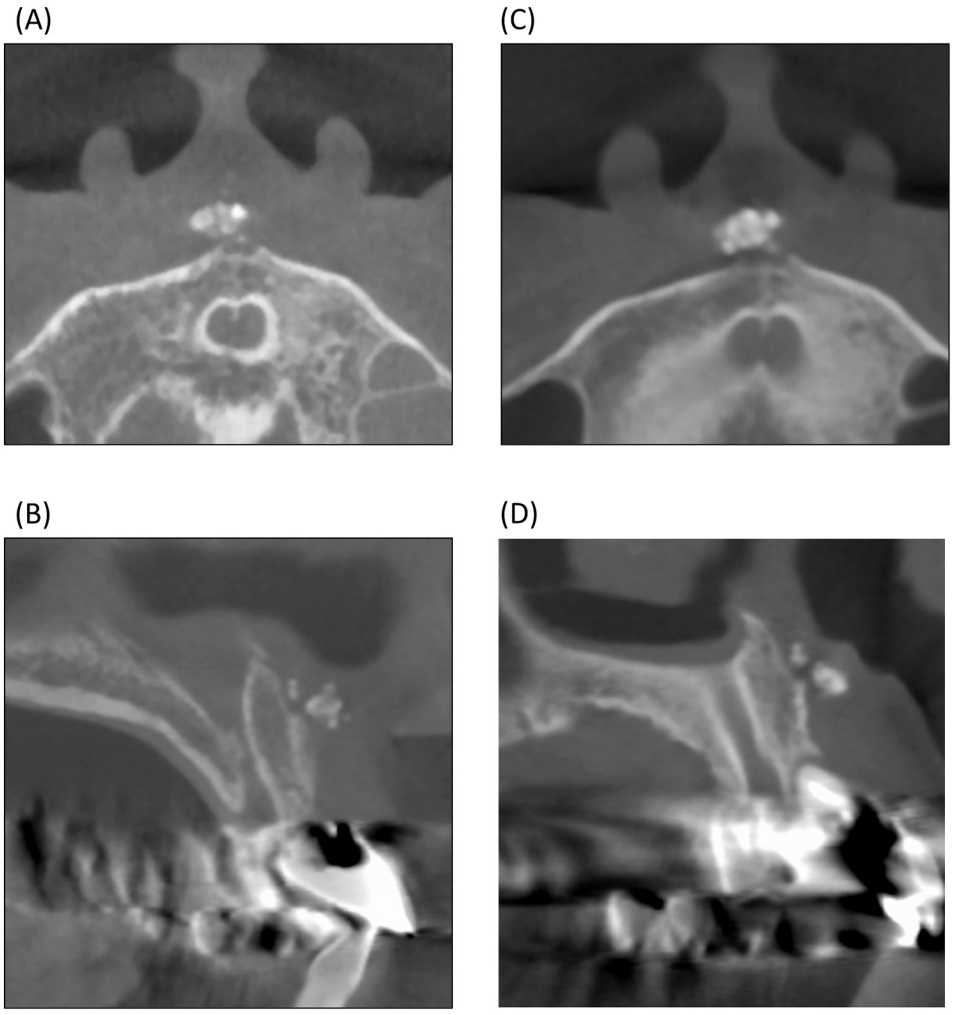

Fig. 4. CBCT images at nasal spine in Patient 3.
Calcifications were evaluated by CBCT in Patient 3 in June 2018 (A, B) and May 2021 (C, D). Calcifications on CBCT images did not change between 2018 and 2021. CBCT, cone-beam computed tomography.

Table 4
Size of calcification and bone-like tissue at nasal spine.

		Length (mm)	Width (mm)	Height (mm)
Patient 1 (Fig. 1)	05/12/2017 (A, C)	5.0	11.6	7.4
	04/15/2021 (B, D)	5.4	10.3	6.5
Patient 2 (Fig. 3)	08/20/2018 (A, C)	5.5	4.3	5.5
	06/11/2021 (B, D)	6.6	5.7	5.9
Patient 3 (Fig. 4)	06/08/2018 (A, C)	4.3	6.5	6.4
	05/13/2021 (B, D)	3.5	6.7	5.3

calcification. Moreover, depending on the direction of the section, perfect matching can be difficult. In this report, only CBCT was acquired to avoid repeated irradiation, but CT is necessary for accurate quantification.

4. Conclusions

We report two cases of bone-like tissue replacement observed in the nasal spine in SSc patient with MERR. A blood test revealed no abnormalities in bone-related factors.

Calcinosis in the maxillofacial area in SSc patient with MERR need to be examined carefully.

Table 5
Laboratory tests.

	Patient 1	Patient 2	Reference range
Bone alkaline phosphatase (μg/L)	21.8	8.5	3.8–22.6
Calcium (mg/dL)	9	9.6	8.7–10.1
Phosphate (mg/dL)	4.2	4	2.8–4.6
1,25-dihydroxyvitamin D (pg/mL)	70	31	20–60
Intact parathyroid hormone (pg/mL)	48.1	44.8	15–65

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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