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Case Report

Two Cases of Frontal Variation of Idiopathic Calvarial Thinning—Therapeutic Effect of Denosumab and Romosozumab

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Abstract

Idiopathic calvarial thinning is a rare condition that causes progressive, painless thinning of the skull bones without systemic disease. We present 2 cases of idiopathic calvarial thinning involving the bifrontal region. Both patients exhibited forehead depression and had normal biochemical tests except for mild vitamin D deficiency. The first patient received treatment with denosumab for 3 years, showing no further progression of the skull thinning. The second patient was treated with denosumab for 3 years, followed by romosozumab for 1 year, resulting in no further progression and even slight recovery of the skull thickness. These cases demonstrate that idiopathic calvarial thinning can involve the bifrontal region and highlight the favorable treatment and prognosis with denosumab or romosozumab.

Key Words: idiopathic calvarial thinning, bifrontal osteodystrophy, bilateral thinning of the frontal bones, osteoporosis, denosumab, romosozumab

Abbreviations: BCT, brain computed tomography; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; WBBS, whole-body bone scan.

Introduction

Calvarial thinning can result from various causes, including congenital syndromes, secondary involvement of systemic diseases such as primary and metastatic tumors, Gorham-Stout disease, hyperparathyroidism, granulomatous disease, diabetes mellitus, osteomyelitis, systemic mastocytosis, aseptic necrosis, bone aneurysm, and cystic angiomatosis of bone [1].

Some cases present as idiopathic calvarial thinning, also known as biparietal osteodystrophy, bilateral parietal thinning, or bilateral thinning of the parietal bones [2]. It is a rare condition, with only around 150 cases reported in the literature [1-8]. It is an acquired disease that progresses slowly, potentially leading to perforation, and spontaneous remission has not been reported so far. It is more common in women than in men, with a prevalence of 0.25% to 0.8% [3]. The characteristic site of thinning is the posteromedial part of the parietal bones [4]. The etiology, pathophysiology, treatment, and prognosis of this condition are unknown.

In this report, we present 2 cases of idiopathic calvarial thinning with the involvement of the bifrontal region. We also discuss the therapeutic effects of denosumab and romosozumab in idiopathic calvarial thinning.

Case Presentation

Case 1

A 61-year-old woman with no significant previous medical history was referred due to progressive, painless, multiple dimpling in her forehead over the past 5 years. Her family history was unremarkable for any hereditary bone disease. The forehead depression was symmetric in the frontal region, approximately 3 cm in diameter, with circular contours and grossly normal overlying skin (Fig. 1A).

A plain x-ray of the skull revealed multiple irregular skull defects in both frontal bones. On brain computed tomography (BCT), the skull defect had a thickness of 2.76 mm at its thinnest locus. Bone thickness measured according to the protocol by Sanati-Mehrizy (2020) is provided in Table 1 [5]. Dual-energy x-ray absorptiometry (DXA) showed osteopenia with a femur neck bone mineral density (BMD) of −2.3. Bone scan and single-photon emission computed tomography (SPECT-CT) revealed 2 frontal bone dimplings with decreased radiotracer uptake but no site of increased uptake. Biochemical tests were within normal ranges except for mild vitamin D deficiency, including calcium (8.6 mg/dL, 2.15 mmol/L; reference interval, 8.5-10.5 mg/dL, 2.13-2.63 mmol/L), phosphate (4.1 mg/dL, 1.32 mmol/L; reference interval, 2.8-4.5 mg/dL, 0.90-1.45 mmol/L), alkaline phosphatase (71 IU/L, 1.17 μkat/L; reference interval, 50-155 IU/L, 0.83-2.59 μkat/L), c-telopeptide (0.503 ng/mL, 503 pg/mL; reference interval, 0-1.008 ng/mL, 104-1008 pg/mL), procollagen type 1N-terminal propeptide (36.5 ng/mL, 36.5 μg/L; reference interval, 22.9-126.0 ng/mL, 22.9-126.0 μg/L), 25-OH-vitamin D (18.51 ng/mL, 46.20 nmol/L; reference interval, 30-100 ng/mL, 74.88-249.60 nmol/L), and parathyroid hormone (41.6 pg/mL, 41.6 ng/L; reference interval,

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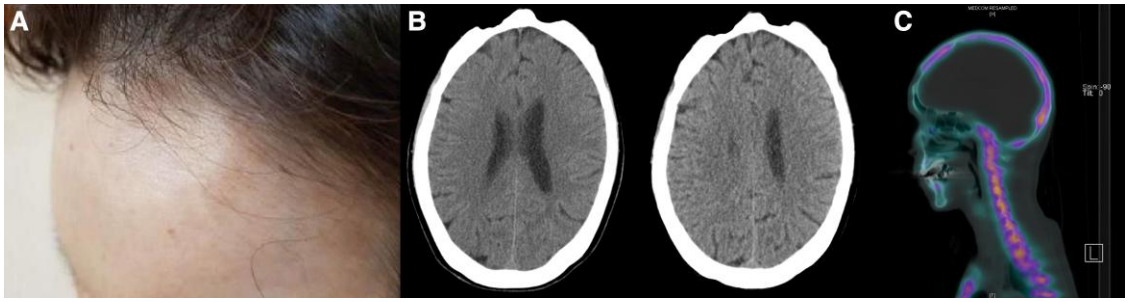

Figure 1. Imaging diagnosis of case 1. A, Gross imaging shows a dimpling of her left forehead. B, Initial brain computed tomography (CT) (left) and follow-up brain CT (right) after 2 years of denosumab. Bone thickness measured according to protocol by Sanati-Mehrizy (2020) [5] is provided in Table 1. C, SPECT-CT revealed bone dimpling with heterogeneous radiotracer uptake in the entire skull.

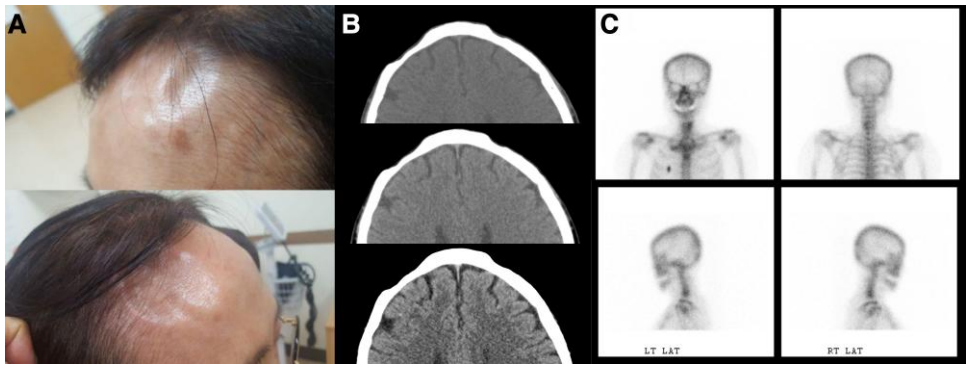

Figure 2. Imaging diagnosis of case 2. A, Gross imaging shows asymmetric skull dimpling of her foreheads. B, Initial brain computed tomography (CT), 2 years' follow-up brain CT after 2 years of denosumab, and 4 years' follow-up brain CT after 3 years of denosumab followed by 1 year of romosozumab. Bone thickness measured according to protocol by Sanati-Mehrizy (2020) [5] is provided in Table 1. Initial skull defect of 3.34 mm at its deepest defect, 2.86 mm at 2 years' follow-up CT and 6.03 mm at 4 years' follow-up CT, showing gradual improvement. C, Whole-body bone scan showed decreased uptake in the right frontal bone.

15-65 pg/mL, 15-65 ng/L). Overall, the patient was classified as stage III thinning according to Cederlund (1982) [4].

Case 2

A 63-year-old woman with no significant previous medical history was referred due to progressive, painless dimpling in her right forehead over the past 3 years. There was no remarkable family history. The forehead depression was observed in the right frontal region, approximately 3 cm in diameter, with an irregular and ovoid contour. Recent progression was also noted on her left frontal region, with a smaller dimpling of approximately 1 cm in diameter and with an ovoid contour (Fig. 2A).

The imaging study showed 2 focal areas of skull thinning. On the BCT, the right skull defect had a thickness of 3.34 mm at its thinnest locus. Whole-body bone scan (WBBS) showed decreased uptake in the right frontal bone but no other abnormal increased uptake. DXA revealed osteopenia with a T-score of −2.2 on the femur neck. Like case 1, biochemical tests were within normal ranges except for mild vitamin D deficiency, including calcium (9.3 mg/dL, 2.33 mmol/L; reference interval, 8.5-10.5 mg/dL, 2.13-2.63 mmol/L), phosphate (3.5 mg/dL, 1.13 mmol/L; reference interval, 2.8-4.5 mg/dL, 0.90-1.45 mmol/L), alkaline phosphatase (87 IU/L, 1.45 μkat/L; reference interval, 50-155 IU/L, 0.83-2.59 μkat/L), c-telopeptide (0.325 ng/mL, 325 pg/mL; reference interval, 0-1.008 ng/mL, 104-1008 pg/mL), procollagen type 1N-terminal propeptide (40.0 ng/mL, 40.0 μg/L; reference interval, 22.9-126.0 ng/mL, 22.9-126.0 μg/L), 25-OH-vitamin D (13.60 ng/mL, 33.95 nmol/L; reference interval, 30-100 ng/mL, 74.88-249.60 nmol/L), and parathyroid hormone (50.4 pg/mL, 50.4 ng/L; reference interval, 15-65 pg/mL, 15-65 ng/L). Bone thickness measured according to protocol by Sanati-Mehrizy (2020) is provided in Table 1, and the patient was classified as stage II thinning according to Cederlund (1982) [4, 5].

Treatment

Case 1

Patient 1 received treatment with denosumab every 6 months for 3 years, for a total of 6 doses.

Case 2

Patient 2 received treatment with denosumab for 3 years, a total of 7 doses, followed by romosozumab for 1 year, for a total of 12 doses.

Both patients took daily oral calcium carbonate/cholecalciferol 100 mg/1000 IU throughout the treatment. Vitamin D level was regularly measured and replaced with cholecalciferol injection if necessary.

Outcome and Follow-up

Case 1

In case 1, BCT was performed after 2 years of treatment (after 3 doses of denosumab). The patient complained of no

Table 1. Measured bone thickness

Case 1, mm	R3	R2	R1	M	L1	L2	L3
Initial	9.85	3.17	8.74	9.22	7.32	2.76	10.65
2-y follow-up	11.66	4.25	10.72	10.82	10.31	3.44	12.1
Case 2, mm	**R3**	**R2**	**R1**	**M**	**L1**	**L2**	**L3**
Initial	7.32	3.34	7.58	8.9	9.16	4.58	6.48
2-y follow-up	6.73	2.86	8.31	9.16	8.9	5.29	6.68
4-y follow-up	7.52	6.03	9.43	9.85	9.89	7.01	8.09

Bone thickness measured at 7 points of interest adopted from Sanati-Mehrizy (2020) [5], in the axial view of brain computed tomography.
Abbreviations: L1, thickness of surrounding calvarium on the medial side of the defect on the left; L2, thinnest point of left defect; L3, thickness of surrounding calvarium on the lateral side of the defect on the left; M, midline; R1, thickness of surrounding calvarium on the medial side of the defect on the right; R2, thinnest point of right defect; R3, thickness of surrounding calvarium on the lateral side of the defect on the right.

progression, showing a thickness of 4.35 mm at the follow-up BCT (Fig. 1B).

Case 2

In case 2, bone thickness was measured by BCT after 2 years of treatment (after 3 doses of denosumab) and after 4 years of treatment (after 7 doses of denosumab and 12 doses of romosozumab). The patient complained of no progression before romosozumab and improvement of dimpling after romosozumab. The scalp dimpling showed no further progression, and even slight recovery with an increased thickness of 6.03 mm after 1 year of romosozumab (Fig. 2B).

Discussion

We presented 2 cases of idiopathic calvarial thinning in patients without evidence of systemic disease. Though it is typically known to affect the area between the sagittal suture and the parietal prominence, our cases demonstrate that it can also involve the bifrontal region of the skull [5].

Idiopathic calvarial thinning is an uncommon condition, with only a handful of reports documenting approximately 150 cases to date [1-7]. Previous studies have reported cases of slow progression and even death due to symmetrical perforation of the affected skull [2]. In 2 case reports, cranioplasty was performed to prevent exposure of the brain to atmospheric pressure [1, 7]. Only 1 case report explored the use of alendronate for treatment in 3 patients, but it did not provide data about the effect on skull thickness and only showed BMD by DXA. Among 3 patients, only 1 case showed improvement in skull BMD.[6]

Our case series shows that treatment and prognosis for idiopathic calvarial thinning are generally favorable when managed with antiosteoporosis treatment, with patients experiencing no further progression of the thinning proven with BCT.

Both patients had mild vitamin D deficiency. However, we believe that mild vitamin D deficiency is unlikely to be the cause of calvarial thinning in these patients. Vitamin D deficiency is relatively common in South Korea [9]. To our knowledge, no cases have previously reported vitamin D deficiency associated with focal osteomalacia or rickets. Additionally, parathyroid hormone and bone turnover markers, including c-telopeptide and procollagen type 1N-terminal propeptide, were within normal ranges, which is less likely if the calvarial thinning had been related to vitamin D deficiency.

Differential diagnosis includes Gorham-Stout disease and mastocytosis. Gorham-Stout disease is characterized by spontaneous and progressive osteolytic lesions in a single bone or multiple bones. In Gorham-Stout disease, BCT reveals radiolucent foci in the intramedullary or subcortical regions and WBBS shows increased uptake around the margin and decreased uptake in the diminished bone region [10]. These did not match the patients' images finding and Gorham-Stout disease was ruled out. Mastocytosis was also ruled out because our patients did not show any typical clinical features such as rash or gastrointestinal symptoms. We believe that the diagnosis of idiopathic calvarial thinning can be made if there is no evidence of other systemic disease in routine laboratory tests, CT, and bone scintigraphy. Brain magnetic resonance imaging and/or pathologic confirmation can be considered but would not be necessary.

Histologic examination in previous studies showed homogenously affected membranous bone tissue with regressed diploe, and absence of either osteoblasts or osteoclasts [1]. This might suggest that idiopathic calvarial thinning might be due to osteoporosis and decreased bone formation rather than increased bone destruction, which also coincides with WBBS findings [4]. Thus, besides the strong antiresorptive agents, such as denosumab, we have tried strong anabolic therapy, such as romosozumab in idiopathic calvarial thinning. If romosozumab is not feasible, due to concerns about rapid bone loss and possible calvarial perforation after denosumab use, sequential use of bisphosphonate might be considered.

These cases serve to illustrate the clinical presentation, imaging findings, and treatment options for idiopathic calvarial thinning. Although this condition is rare, it can be cautiously managed with denosumab or romosozumab as most of the patients also show low bone mass as well.

Learning Points

- Idiopathic calvarial thinning is a rare, acquired, slowly progressing disease that causes idiopathic skull thinning without evidence of systemic disease.
- It is characterized by the thinning of the skull bone, which can lead to painless dimpling or depressions in the scalp. Though it is known to affect the area between the sagittal suture and the parietal prominence, it can also affect the bifrontal skull.

- Progression of skull thinning can be cautiously managed with denosumab or romosozumab.

Contributors

All authors made individual contributions to authorship. N.H. and Y.R. were involved in the diagnosis and management of this patient and manuscript submission. S.B. drafted and edited the manuscript. N.H. and Y.R. contributed to the editing of the manuscript. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patients.

Data Availability Statement

Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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