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Original article

Novel fully interconnected porous hydroxyapatite ceramic in surgical treatment of benign bone tumor

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Abstract

Background. Large bone defects remaining after curettage of benign bone tumors should be filled with a substitute to restore mechanical strength. In 2000, we developed a fully interconnected porous calcium hydroxyapatite ceramic (IP-CHA, NEOBONE) and have utilized it as a bone substitute. IP-CHA has a finely organized, three-dimensional interconnecting pore structure. The large interconnecting channels (average diameter 40 μm) permit easy penetration of tissue into the deep pores, so IP-CHA can itself induce local bone repair processes. The purpose of this study was to evaluate the clinical outcomes with the use of IP-CHA as bone substitute after curettage of benign bone tumors.

Methods. We reviewed the results of 71 patients with benign bone tumors sequentially treated by curettage followed by implantation of IP-CHA between 2000 and 2006. There were 29 women and 42 men, with a mean age of 28 years. Assessment was based on radiography at each time point during the follow-up. Radiographic findings were classified into five stages: stage 0, no change; stage 1, slight bone formation; stage 2, moderate bone formation; stage 3, consolidation; stage 4, absorption.

Results. In 70 of 74 operated lesions, radiographs showed that implanted IP-CHA proceeded to stage 2 or more within an average of 8 months after the surgery. In addition, 17 lesions proceeded to stage 4 within 35 months after surgery, on average. However, there were 10 local recurrences, which is similar to the recurrence rate for such tumors treated with or without implantation of CHAs and reflects the biological nature of each tumor.

Conclusions. In this study, we utilized IP-CHA as a bone substitute after curettage of benign bone tumors and demonstrated its usefulness in the clinical situation. IP-CHA comparatively exhibited excellent bone formation at an early stage although the problem of recurrence of the tumor remained. We conclude that IP-CHA is a useful bone substitute for the treatment of benign bone tumors.

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Introduction

When bone grafts are required for bone defects in orthopedic surgery, autogenous bone grafting has been the gold standard because of its osteogenic potential, mechanical properties, and the lack of adverse immunological response. However, autogenous bone grafting has some limitations, such as the additional surgery needed for harvesting, the limited availability of grafts of sufficient size and shape, and the risk of donor site morbidity,[1] such as long-lasting pain, fracture, nerve damage, and infection. Therefore, biomaterials have been developed as bone substitutes, including hydroxyapatite (HA), alumina, zirconia, polymers, metal, and organic or nonorganic bone substitutes.[2]

Hydroxyapatite ceramics have been used extensively as a substitute in bone grafts[3] because the crystalline phase of natural bone is similar to that of HA. Since the 1980s, "first-generation" porous calcium hydroxyapatite ceramics (CHA) have been used in orthopedic, dental, and craniofacial surgery.[4,5] However, there are few reports showing that the pores of implanted CHA were totally filled with the newly formed host bone probably owing to the closed structures of the previous CHA with few interpore connections.[6]

Therefore, the development of a "second-generation" porous CHA with interpore connections of adequate diameter as well as adequate strength has long been anticipated as the ideal bone substitute. We recently developed fully interconnected porous CHA (IP-CHA) with a porosity of 75%, an average pore size diameter of 150 mm, and average interconnections of 40 mm in diameter by adopting a "form-gel" technique.[7] The interconnected porous structure facilitates bone tissue engineering by allowing the introduction of mesenchymal cells, osteotropic agents, and vasculature into the pores (Fig. 1). We report a series of 71 patients with benign bone tumors followed for an average of 35

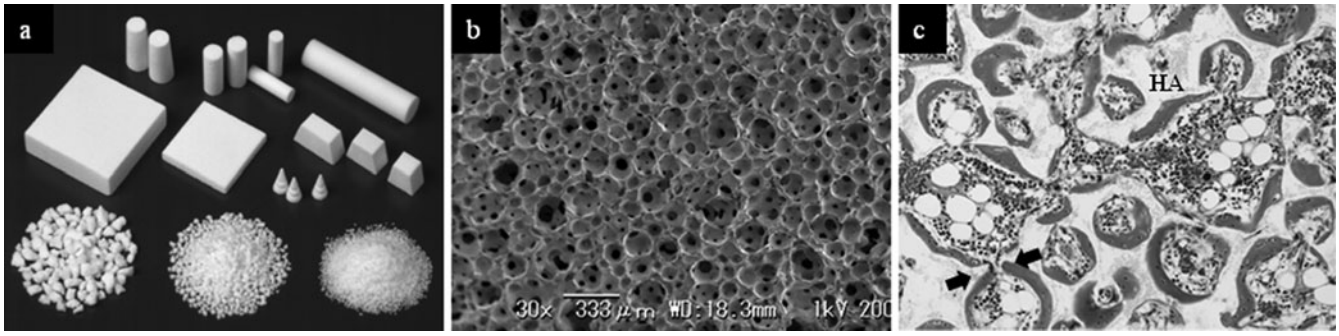

Fig. 1. Macroscopic and microscopic views of interconnected porous calcium hydroxyapatite ceramic (IP-CHA) and histological analysis of new bone formation in the rabbit femoral condyle. **a** Macroscopic view of IP-CHA. **b** Scanning electron microscopy (SEM) of the microstructures of IP-CHA. Spherical pores (100–200 mm diameter) were divided by thin walls and interconnected by interpores (10–80 mm diameter). **c** New bone formation within the IP-CHA in the rabbit femoral condyle model. Active bone formation and bone marrow formation that passed through the interconnections (*arrows*) are observed. *White area* shows the ghost of decalcified hydroxyapatite (*HA*) ceramics. The newly formed bone was rimmed by cuboidal active osteoblasts. H&E, ×100

months after treatment with curettage followed by IP-CHA implantation.

Patients and methods

We retrospectively reviewed the results of 71 patients with benign bone tumors sequentially treated with curettage followed by implantation of IP-CHA (Covalent Materials, Tokyo, Japan) between 2000 and 2006. Among them, five patients underwent revision surgery for recurrence (three patients were retreated with IP-CHA, and two were retreated with other methods); consequently, radiographic investigations were performed on 74 operated lesions of 71 patients (Table 1). There were 29 women and 42 men in our study, with a mean age of 28 years.

The histological diagnoses were as follows: enchondroma in 19 patients, simple bone cyst (SBC) in 12 patients, giant cell tumor of bone (GCT) in 12 patients, chondroblastoma in 9 patients, intraosseous ganglion in 6 patients, fibrous dysplasia (FD) in 5 patients, osteofibrous dysplasia (OFD) in 2 patients, intraosseous lipoma in 2patients, aneurysmal bone cyst (ABC) in 1 patient, nonossifying fibroma (NOF) in 1 patient, eosinophilic granuloma (EG) in 1 patient, and osteoid osteoma in 1 patient. The tumor locations were as follows: 19 were in the femur, 11 in the phalanx, 8 in the tibia, six in the humerus, 5 in the pelvis, 4 in the calcaneus, 4 in the metacarpal, 3 in the ulna, 3 in the metatarsal, 2 in the radius, 1 in the scapula, 1in the patella, 1 in the fibula, 1 in the talus, 1 in the cuneiform, and 1 in the navicular bone. All the lesions were imaged and evaluated by plain radiography. The mean follow-up period was 35 months (range 12–92 months).

Second-generation synthetic IP-CHA

The conventional method used to manufacture synthetic porous HA ceramic is by sintering an HA slurry mixed with organic polymer beads. The polymer beads melt and vaporize during the sintering process, eventually leaving pores in the ceramic material. However, the pores resulting from this method are irregular in size and shape and are not fully interconnected with one another. Together with Covalent Materials Co., MMT Co., and the National Institute for Materials Science, Biomaterials Center, we recently developed IP-CHA (NEOBONE), which has a porosity of 75%, an average pore size diameter of 150 mm, and an average interpore connections diameter of 40 mm. We accomplished it by adopting the "foam-gel" technique.[7] This approach involves a cross-linking polymerization step that rapidly gelatinizes the foam-like CHA slurry, thus promoting the formation of an interconnected porous structure. Briefly, the new manufacturing method consists of the following steps.

1. Slurry preparation. Slurry was prepared by mixing HA (60 wt%) with a cross-linking substrate (polyethyleneimine 40 wt%).
2. Foaming and gelatinization. The slurry was mixed with a foaming agent (polyoxyethylene lauryl ether 1 wt%) and stirred until the mixture had a foamy appearance. The pore size was controlled by regulating the stirring time.
3. Gelatinization. To gelatinize the foamed slurry, another water-soluble cross-linking agent (poly functional epoxy compound) was added, and the mixture was cast by pouring it into a mold. The porous structure stabilized in less than 30 min. The foamy HA gel was removed from the mold, dried, and sintered at 1200°C.

Table 1. Details of 74 operated lesions in 71 patients with benign bone tumors treated with curettage followed by implantation of IP-CHA

Patient no.	Operation no.	Age (years)	M/F	Bone	Site in bone	Diagnosis	IP-CHA volume (g)	Recurrence	Reoperation	Follow-up (months)	Final stage
1	1	46	F	Metacarpal	D, M	Enchondroma	<1	–		92	3
2	2	32	M	p-Phalanx	M, E	Enchondroma	<1	–		87	3
3	3	52	F	d-Phalanx	M, E	Enchondroma	<1	–		81	4
4	4	54	M	Metacarpal	M, E	Enchondroma	<1	–		59	4
5	5	54	F	p-Phalanx	D, M	Enchondroma	<1	–		56	3
6	6	59	F	p-Phalanx	D	Enchondroma	<1	–		55	4
7	7	10	M	p,m-Phalanx	D	Enchondroma	<1	–		47	4
8	8	18	F	p-Phalanx	D	Enchondroma	<1	–		42	4
9	9	13	F	Metatarsal	D	Enchondroma	<1	–		41	4
10	10	28	M	m-Phalanx	D, M	Enchondroma	<1	–		27	4
11	11	30	F	Metacarpal	M	Enchondroma	<1	–		24	3
12	12	33	M	m-Phalanx	D, M, E	Enchondroma	<1	–		23	3
13	13	73	M	Fibula	M, E	Enchondroma	5	–		21	2
14	14	33	F	Metatarsal	M	Enchondroma	<1	–		18	3
15	15	28	M	p-Phalanx	M, E	Enchondroma	<1	–		18	3
16	16	26	M	m-Phalanx	D	Enchondroma	<1	–		18	4
17	17	21	M	p-Phalanx	D, M	Enchondroma	<1	–		14	2
18	18	44	M	Metacarpal	M, E	Enchondroma	<1	–		14	2
19	19	61	F	Tibia	D, M	Enchondroma	10	–		24	2
20	20	4	M	Femur	M	SBC	5	–		61	4
21	21	21	M	Femur	M	SBC	30	–		54	3
22	22	15	M	Humerus	D, M	SBC	30	–		53	4
23	23	16	M	Calcaneus	—	SBC	6	–		41	3
24	24	8	F	Radius	M	SBC	2	+	–	41	3
25	25	12	M	Humerus	D, M	SBC	12	+	+	11	3
25	26	12	M	Humerus	D, M	SBC	12	–		40	4
26	27	3	M	Radius	M	SBC	1	+	–	39	3
27	28	16	F	Humerus	D	SBC	10	–		32	4
28	29	5	F	Humerus	D, M	SBC	10	–		28	4
29	30	14	M	Pelvis	—	SBC	10	–		22	4
30	31	19	F	Ulna	M	SBC	5	+	+	14	3
30	32	19	F	Ulna	M	SBC		–		21	3
31	33	5	M	Femur	M	SBC	3	+	–	18	3
32	34	21	M	Femur	E	GCT	25	+	–	61	0
33	35	43	F	Femur	E	GCT	40	–		60	3
34	36	19	M	Pelvis	—	GCT	5	–		53	4
35	37	58	F	Pelvis	—	GCT	4	–		50	3
36	38	40	M	Humerus	E	GCT	20	–		39	3
37	39	57	F	Femur	E	GCT	30	–		35	3
38	40	51	M	Tibia	E	GCT	10	–		31	3
39	41	54	M	Femur	E	GCT	30	+	+	27	0
40	42	61	M	Femur	E	GCT	19	–		21	0
41	43	42	M	Tarsal	—	GCT	1	–		20	3
42	44	21	F	Femur	E	GCT	25	–		15	3
43	45	45	M	Ulna	E	GCT	3	–		12	2
44	46	22	M	Talus	—	Chondroblastoma	10	–		57	4
45	47	10	F	Tibia	E	Chondroblastoma	1	–		50	3
46	48	22	M	Pelvis	—	Chondroblastoma	30	–		49	3
47	49	31	M	Calcaneus	—	Chondroblastoma	20	+	+	41	0
47	50	35	M	Calcaneus	—	Chondroblastoma	13	–		16	2
48	51	21	M	Femur	E	Chondroblastoma	20	–		36	3
49	52	24	M	Calcaneus	—	Chondroblastoma	5	–		27	3
50	53	16	M	Pelvis	—	Chondroblastoma	17	–		24	3
51	54	22	M	Patella	—	Chondroblastoma	1	–		21	3
52	55	13	F	Femur	E	Chondroblastoma	2	–		12	3
53	56	40	F	Metatarsal	D	Ganglion	<1	–		58	3
54	57	11	M	Navicular	—	Ganglion	<1	–		44	3
55	58	13	M	Femur	E	Ganglion	1	–		25	3

Table 1. Continued

Patient no.	Operation no.	Age (years)	M/F	Bone	Site in bone	Diagnosis	IP-CHA volume (g)	Recurrence	Reoperation	Follow-up (months)	Final stage
56	59	17	M	Femur	E	Ganglion	2	–		24	3
57	60	41	F	Tibia	E	Ganglion	1	–		19	2
58	61	39	M	Scapula	—	Ganglion	1	–		12	3
59	62	29	F	Femur	M	FD	20	+	–	65	3
60	63	13	M	Tibia	D	FD	10	–		46	4
61	64	30	F	Ulna	D	FD	1	–		39	3
62	65	19	F	Femur	M	FD	17	+	+	22	3
63	66	42	M	Humerus	M	FD	5	–		19	2
64	67	23	F	Tibia	D	OFD	8	–		35	3
65	68	25	F	Tibia	D	OFD	2	–		27	3
66	69	38	F	Calcaneus	—	Lipoma	6	–		49	3
67	70	23	M	Femur	M	Lipoma	10	–		21	4
68	71	10	M	Femur	D	ABC	17	–		35	4
69	72	13	M	Tibia	M	NOF	5	–		23	3
70	73	21	F	Femur	D	EG	3	–		12	3
71	74	17	M	Femur	E	Osteoid osteoma	3	–		12	3

IP-CHA, interconnected porous calcium hydroxyapatite ceramic; p-, proximal; m-, middle; d-, distal; E, epiphysis; M, metaphysis; D, diaphysis; SBC, simple bone cyst; GCT, giant cell tumor; FD, fibrous dysplasia; OFD, osteofibrous dysplasia; ABC, aneurysmal bone cyst; NOF, nonossifying fibroma; EG, eosinophilic granuloma

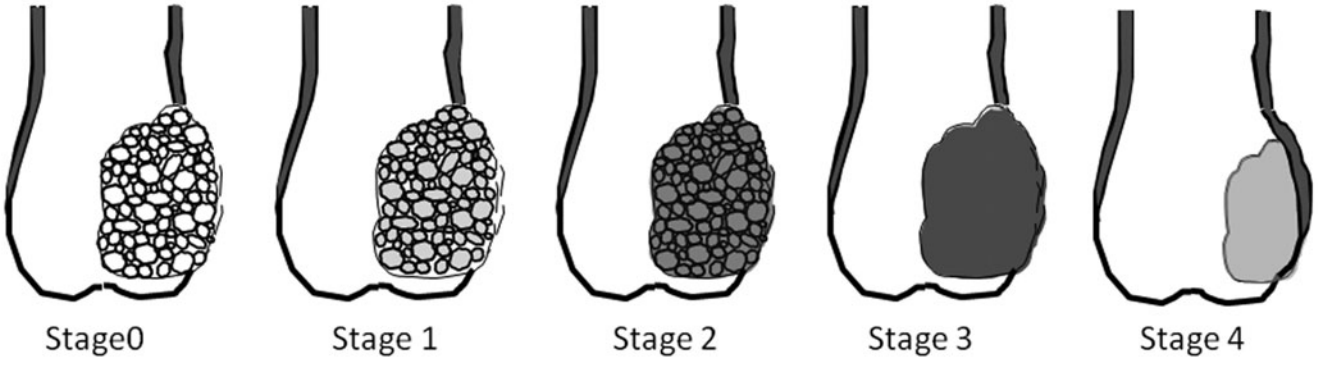

Fig. 2. Radiographic staging: stage 0, no bone formation in the IP-CHA; stage 1, slight bone formation in the IP-CHA with radiolucency superior to that of neighboring cortical bone; stage 2, moderate bone formation in the IP-CHA with radiolucency less than or equal to that of neighboring cortical bone; stage 3, consolidation stage with diffuse sclerosis such that the outline of the IP-CHA granules cannot be confirmed; stage 4, absorption stage with absorption of the IP-CHA or remodeling of the bone marrow cavity

Operative technique

The tumor was exposed through an appropriately sized bone window, and careful curettage was performed using a curette. Granule-type IP-CHA was filled and pressed into the bone defect with original equipment (pushers, slides, and funnels) in all 74 operated lesions. In four operated lesions, block-type IP-CHA was used for rigid augmentation. In two operated lesions, internal fixation using plates and screws was used because of a pathological fracture found at the first medical examination.

Assessment and statistical analysis

Assessment was performed based on clinical examination and plain radiography at the time of each follow-up. All assessments were performed by two musculoskeletal tumor service staff members of Osaka University who were blinded to the clinical conditions. Because IP-CHA is characterized by sclerotic change on plain radiography owing to its superior osteoconductivity, we modified Matsumine's radiographic staging.[4] As shown in Fig. 2, radiographic findings were classified into five stages, which focused on bone formation in the implanted

IP-CHA as follows: stage 0, without any bone formation in the IP-CHA; stage 1, slight bone formation in the IP-CHA, with radiolucency superior to that of neighboring cortical bone; stage 2, moderate bone formation in the IP-CHA, with radiolucency less than or equal to that of neighboring cortical bone; stage 3, consolidation stage characterized by diffuse extensive sclerosis such that one is unable to confirm the outline of the IP-CHA granules; and stage 4, absorption stage (absorption of the IP-CHA or remodeling of the bone marrow cavity). To ensure the consistency, we adopted the stage (0–4) that could be confirmed twice or more on two directional plain radiographs.

Statistical analyses were performed using JMP statistical software (version 7; SAS Institute, Cary, NC, USA). Comparisons between two groups were made by Pearson's χ^2 test. Univariate analyses were performed using the Mann-Whitney U-test for nonparametric data. A difference of $P < 0.05$ was considered significant.

Each author certifies that his or her institution had approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.

Results

Clinical findings

No adverse events such as postoperative fracture, infection, allergic reaction, or toxicity occurred in any patient. There were 10 local recurrences of tumor: 5 in the group with an SBC, 2 in the group with GCT of bone, 2 in the group with FD, and 1 in the group with chondroblastoma. Among them, five patients advanced to reoperation because of the recurrence: two had an SBC and underwent recurettage (patients 25, 30); one had an aggressive GCT of bone and underwent wide resection reconstructed with a megaprosthesis (patient 39); one had a chondroblastoma and underwent recurettage) (patient 47); and one had FD and underwent recurettage (patient 62) (Table 1).

Radiographic findings

In 70 (95%) of 74 lesions, radiographs showed that the implanted IP-CHA proceeded to stage 2 or more. Four lesions stayed at stage 0 throughout the term of surveillance (34 months on average) and showed relapse on the radiograph in three lesions (two with GCT of bone, one with chondroblastoma). On the other hand, partial bone formation within the IP-CHA could be observed despite of tumor relapse in seven patients with SBC or FD (patients 24, 25, 26, 30, 31, 59, 62) (Table 1).

We performed sequential plotting, which demonstrated the overall transition of the radiographic staging (Fig. 3). The mean periods required to reach each stage were as follows: stage 1 occurred in 3 months (range 1–7 months); stage 2 occurred in 8 months (range 2–45 months); stage 3 occurred in 18 months (range 6–65 months); and stage 4 occurred in 35 months (range 18–81 months). Radiographs at the final follow-up were staged as follows: stage 0 in 4 operated lesions; stage 1 in none; stage 2 in 4; stage 3 in 43; and stage 4 in 19 (Table 1). It must be noted that in no patient was the IP-CHA completely absorbed.

Case 1 (patient 68)

A 10-year-old boy presented with a painful lytic femoral lesion seen on lateral radiographs of the right femur. He

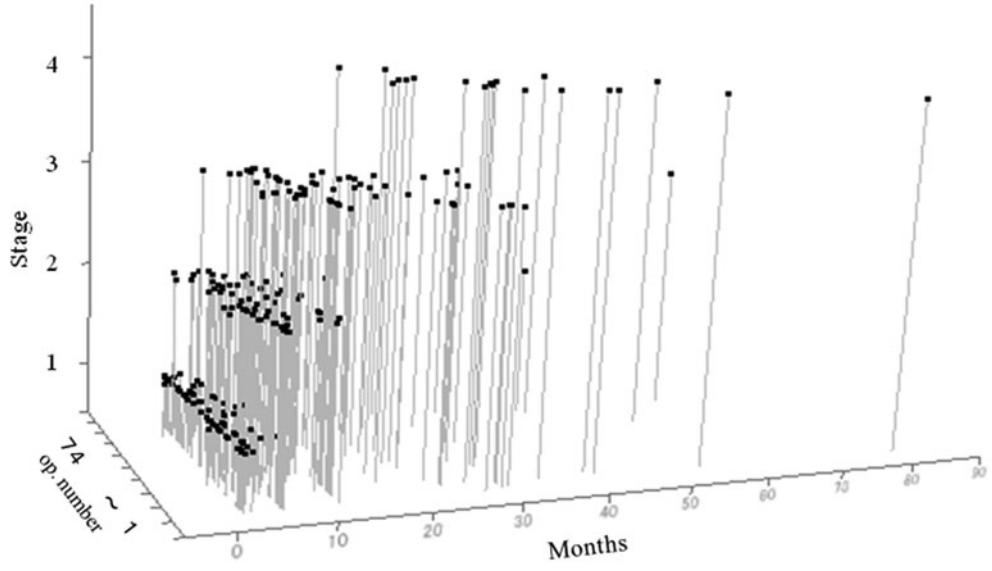

Fig. 3. Overview of the sequential jump-up on radiographic staging (z-axis) for each operated (*op.*) lesion (y-axis). We excluded four operated lesions that remained at stage 0 during the term of the surveillance. The time from stage 3 to stage 4 is the most widespread. The mean periods required to reach each stage were as follows: stage 1 in 3 months (range 1–7 months), 70 lesions; stage 2 in 8 months (range 2–45 months), 70 lesions; stage 3 in 18 months (range 6–65 months), 62 lesions; stage 4 in 35 months (range 18–81 months), 19 lesions

Fig. 4. Case 1. Radiographs of a 10-year-old boy (patient 68) with an aneurysmal bone cyst of the femur show representative stages of the implanted IP-CHA. **a** Lateral view of the diaphysis of the right femur with extensive osteolysis. **b** After operation (stage 0). **c** At 2 months after surgery, IP-CHA shows slight bone formation (stage 1). **d** Moderate bone formation with a granular contour of the implanted IP-CHA at 5 months after surgery (stage 2). **e** "White-out" phenomenon with no granular contour of the implanted IP-CHA at 11 months after surgery (stage 3). **f** Remodeling of the bone marrow cavity at 27 months after surgery (stage 4)

was taken to the operative suite and underwent biopsy, curettage, and packing with 10 g of IP-CHA granules. A diagnosis of aneurysmal bone cyst was made. At 2 months after surgery, a slight increase in the density of the implanted IP-CHA granules and partial disappearance of the radiolucent lines between implant and host bone (Fig. 4c) (stage 1) were observed. At 5 months after surgery, a marked increase in density with distinct outline of the implanted IP-CHA, which was superior to the cortical bone, was observed (Fig. 4d) (stage 2). The patient had diffuse "white-out" bone formation (Fig. 4e) (stage 3) at 11 months after surgery, which resulted in absorption of the implanted IP-CHA and remodeling of the bone marrow cavity 27 months after the surgery (Fig. 4f) (stage 4).

Case 2 (patient 7)

A 10-year-old boy with right proximal and middle phalangeal lesions presented with digital pain and an extracortical mass on magnetic resonance imaging. Histological analysis of an intraoperative biopsy specimen showed enchondroma, so curettage and packing with IP-CHA granules followed. The same observations discussed for case 1 were noted in this patient. In brief, the radiographic density at the implanted sites increased with time; and eventually remodeling of bone marrow cavity could be seen (Fig. 5). Interestingly, this phenomenon was observed in parallel in both the proximal and middle phalanges.

Statistical analysis

Table 2 shows the radiographic staging at the final follow-up in groups 3 and 4. Pearson's χ^2 test demonstrated that the odds ratio of absorption of the implanted IP-CHA was significantly higher for skeletally immature (age ≤ 15 years) patients ($P < 0.05$) and in patients with a diaphyseal lesion of a long tubular bone ($P < 0.01$). Our data do not indicate a significant association between sex, type of bone, volume of the implanted IP-CHA, or duration of the follow-up period. Moreover, univariate analyses with the Mann-Whitney U-test demonstrated that the stage 4 group at final follow-up had advanced to stage 2 or stage 3 significantly earlier than the stage 3 group at final follow-up.

Discussion

Large bone defects remaining after curettage of benign bone tumors should be filled with a substitute to restore mechanical strength. The choices include autogenous bone graft, allograft, ceramic material — CHA or β-tricalcium phosphate (β-TCP) — and polymethylmethacrylate (PMMA) bone cement. The use of PMMA bone cement is considered a safe, effective treatment for aggressive benign bone tumors, and it provides local adjuvant therapy and immediate stability.[8] However, considering its biocompatibility and the difficulty handling it during revision surgery, it appears that a bone substitute that can be replaced by host bone is ideal.

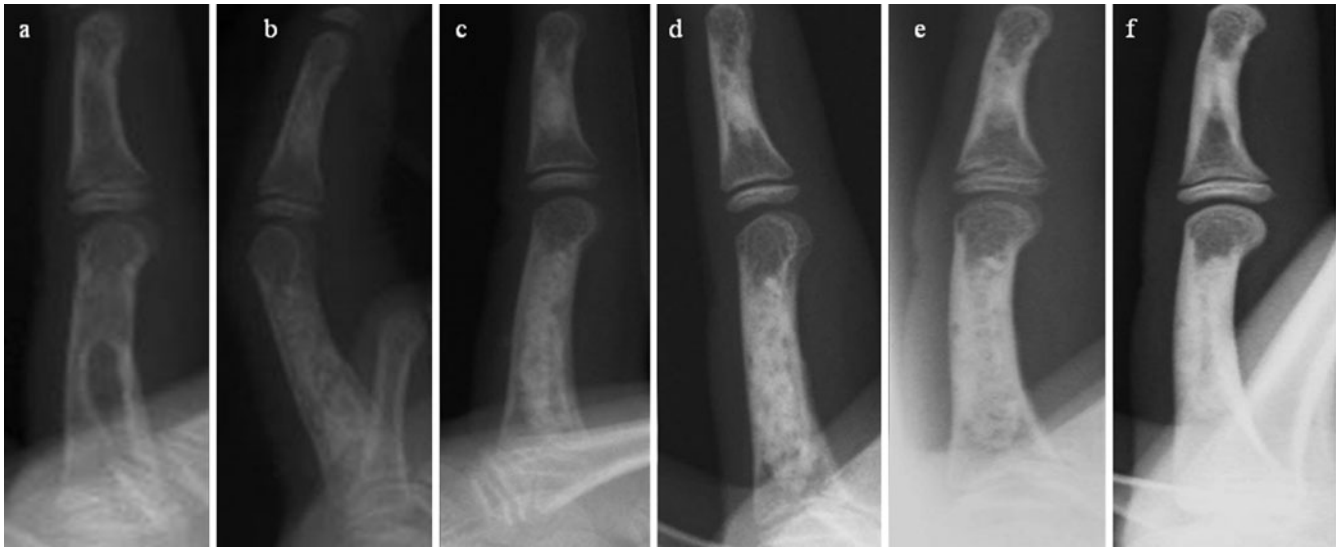

Fig. 5. Case 2. Radiographs of a 10-year-old boy (patient 7) with an enchondroma of the proximal and middle phalanx. **a** Lytic change of the diaphysis. **b** After operation there is increased bone formation in the IP-CHA (stage 0). **c** At 3 months after surgery (stage 1). **d** At 10 months after surgery (stage 2). **e** At 24 months after surgery (stage 3). **f** At 35 months after surgery (stage 4)

Table 2. Relation between radiographic staging at final follow-up and various characteristics

Characteristic	No. of operated lesions	Radiographic staging at final follow-up		*P*
		Stage 3	Stage 4	
Total	62	43	19	
Sex				
Female	27	21	6	0.2
Male	35	22	13	
Age (years)				
≤15	18	9	9	0.0345
>15	44	34	10	
Type of bone				
Long tubular bone	49	33	16	0.5
Non-long tubular bone	13	10	3	
Site in long tubular bone				
Including diaphysis	21	9	12	0.0015
Metaphysis or epiphysis only	28	24	4	
IP-CHA volume (g)				
≤5	37	27	10	0.49
>5	25	16	9	
Follow-up period (months)				
<36	32	25	7	0.12
≥36	30	18	12	
Duration to stage 1	62	3.0 months	2.5 months	0.1
Duration to stage 2	62	8.5 months	5.9 months	0.016
Duration to stage 3	62	18.6 months	14.0 months	0.046

β-TCP is a major bone substitute in Japan, characterized by total or partial resorption at an early phase after surgery. However, its fragility, intraoperative difficulty, and poor postoperative initial strength present problems.[9,10] Therefore, we have utilized several kinds of CHA that are available in Japan for use in massive bone defects after curettage of benign bone tumors and have reported our follow-up studies.[4,5] However, pathological fractures of the implanted sites have been reported as a late complication.[4] These problems are likely due to

poor incorporation of the material into the host bone. If bone formation throughout the porous CHA implant is achieved more quickly, such late complications can be reduced.

In our previous study, we had considerable success in developing IP-CHA that exhibit superior osteoconductivity in vivo.[7,11] Although, the appearance of IP-CHA is apparently similar to other commercial porous CHAs, the structures are not. Scanning electron microscope (SEM) analysis revealed that the pores of IP-CHA are rather spherical, evenly sized (150 mm), regularly lined, and connected to one another with interpore connections (40 mm). This regularly controlled fine structure provides sufficient strength (10 MPa) for clinical use. Commercially available CHAs in Japan for clinical use range from 4.8 to 60.0 MPa, and the compressive strength of cancellous bone ranges from 1 to 12 MPa.[12] Taking the porosity of IP-CHA into consideration, its initial compressive strength is above average. Furthermore, using an animal model, we have demonstrated that the compressive strength increases steadily in parallel with bone ingrowth into the pores.[7]

Clinically, IP-CHA has been used in all fields of orthopedic surgery, including spine surgery and joint surgery.[13,14] Deie et al. reported 12 cases of osteonecrosis of the femoral condyle. They performed IP-CHA grafting with core depression curettage and achieved results comparable to those with other treatments of osteonecrosis, without any complications.[13] Kuriyama et al. reported 10 rheumatoid arthritis patients with juxtaarticular intraosseous lesions. They demonstrated the efficacy of IP-CHA for rheumatoid arthritis and demonstrated sequential bone formation in the implanted IP-CHA.[14] However, our report detailing the bone formation process in implanted IP-CHA in clinical cases is the first of its kind.

Because IP-CHA is a second-generation CHA, unlike conventional CHAs, we were able to focus on the sclerotic change exhibited by the IP-CHA using radiography and incorporated it into our staging paradigm. In 70 of 74 lesions, bone formation in the implanted IP-CHA was equal or superior to the cortical bone in density as shown in the radiographs. Several reports on conventional first-generation CHAs focused only on the incorporation with the surrounding bony tissue, not on the sclerotic change of the CHAs.[15–18] This was because the first-generation CHAs lacked effective interconnected pores and simply appeared as a dense mass on the radiographs. The fact that fine-structured bone formation (stage 1) could be observed radiographically as early as 3 months correlates with our results in the animal experiments.[7] As shown in Fig. 3, the implanted IP-CHA exhibited a stepwise sequential increase until "white out" consolidation in stage 3. For eight lesions that remained in stage 2 at the final follow-up, the follow-up periods were significantly shorter and it is expected that they will eventually advance to stage 3.

Postoperative fracture is a major complication of bone grafting using composite ceramics. Schindler et al. reported that a postoperative fracture occurred in 1 (7%) of 13 patients with composite ceramic bone grafts.[15] Irwin et al. reported two cases (3%) with coralline HA.[17] Other researchers have reported a 3%–4% incidence of bone fracture with CHAs.[4,18] In our study, no postoperative fracture occurred in any of the patients probably owing to the excellent initial compression strength accompanied by superior bone formation in the IP-CHA. In addition, it is easier to time the resumption of weight bearing because it is easy to assess the stage of bone healing with IP-CHA using plain radiographs. Matsumine et al. showed that the mechanical strength of conventional CHA-implanted bone tends to be overestimated because of its dense appearance on radiographs.[4] Schindler et al. reported that the high calcium content and characteristically high density of ceramic bone graft substitutes make it difficult to judge the degree of consolidation.[16]

Bioabsorption of CHA in vivo over time is not completely understood. In our study, 19 (26%) of 74 lesions proceeded to absorption (stage 4), but most showed remodeling of the bone marrow cavity; and in no patient did the implanted IP-CHA disappear completely. Statistical analysis revealed that significant absorption of the IP-CHA was observed in skeletally immature (age ≤ 15) patients ($P < 0.05$) and in patients with diaphyseal lesions of long tubular bone ($P < 0.01$). Generally, absorption of implanted CHA should correlate with normal bone turnover or activity of osteoclasts. Mattori[19] and others[20] gathered detailed information on remodeling activity in the dog and reported that the bone formation rate at the metaphysis was four times higher than in the diaphysis. The absorption of IP-CHA in a diaphyseal lesion is part of the homeostasis of bone marrow remodeling and apparently of the fracture healing process as well.

In our series, although thorough curettage of the tumor was performed, there were 10 local recurrences, which is similar to the recurrence rate for such tumors treated with or without implantation of CHAs and reflects the biological nature of each tumor.[21–23] Interestingly, bone formation of the implanted IP-CHA advanced normally in the case of SBC and FD with recurrences; in contrast, for both GCTs of bone and chondroblastomas with recurrences, no bone formation was observed in the implanted IP-CHA. As the pores of the IP-CHA were fully occupied with recurrent tumor cells in the both GCT of bone and chondroblastoma, it is thought that this was the reason that no bone formation was observed. Conversely, when no bone formation is observed in the implanted IP-CHA, despite a

long follow-up period, in the case of GCT of bone or chondroblastoma, it is thought to be a sign of recurrence of the bone tumor.

Conclusion

IP-CHA is a safe, efficacious bone substitute for filling bone defects after curettage of bone tumor and should be considered as an alternative to autogenous bone.

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