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Clinical, radiological and histological study of the failure of cervical interbody fusions with bone substitutes

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Abstract Few histological studies on bone substitutes in human cervical spine are available and the biological processes of bone substitutes are not well documented. The authors studied four failure cases of cervical interbody fusion: two cases with hydroxyapatite (HA), one case with β -tricalcium phosphate ceramic (β -TCP) and one case with xenograft (bovine bone). Clinical data showed that all the patients experienced neck pain with or without numbness of upper extremity due to fusion failure. Successful fusions were achieved after the salvage surgeries in which autograft were used. Radiographs showed that radiolucent lines were present in all cases. Two HA substitutes fractured without complications. One of them sank into the vertebral body. Some small β -TCP fragments were found under the

microscope. Histological study demonstrated only a few newly formed bones at the interface of the substitutes. The fragments of HA were encapsulated by fibrous tissue. The degradation process and bone regeneration were more active in β -TCP than in HA. The intertrabecular spaces of bovine bone were filled with fibrous tissue. The results suggest that a porous calcium phosphate ceramic with special design might assure bone ingrowth and meet the mechanical requirements in cervical interbody fusion. The complications of these materials in the cervical spine should be highlighted.

Keywords Cervical · Spinal fusion · Tricalcium phosphate · Hydroxyapatite · Xenograft

Introduction

The classic techniques for anterior cervical interbody fusion, reported in the 1950s by Cloward [3] and Smith [21], are widely employed to release the symptoms of cervical spondylosis. Autogenous bone, mostly harvested from iliac crest, is the golden standard for cervical arthrodesis. However, painful complications in the donor site include wound infection, haematoma, chronic pain, increased blood loss and operation time, cutaneous nerve neuroma, and pelvic fracture. Although most of them are minor complications, the incidence could reach as high as 24% [1]. Moreover, autograft bone is limited

in quantity and could not be available in some revision cases. The banked allograft provides an alternative source, but the potential of HIV and other virus transmission still exists.

Nowadays several kinds of bone substitutes, such as calcium phosphate (C-P) ceramics, are available commercially. The synthetic C-P ceramics, possessing similar chemico-physical characteristics as that of human bone, have been used successfully in orthopaedic surgery. They can be used as fillers for long bone defect or as extensors in posterior spinal fusion to reduce the quantity of autogenous bone. In anterior spinal interbody fusion, they can be alternatives to autograft. Their efficiency in

cervical spine has been reported in animal experiments and clinical studies [2, 4, 11, 17, 19]. However, the rigorous mechanical circumstance of cervical spine requires superior C-P ceramics with special structure and high biocompatibility. Do those substitutes meet the rigorous criteria of cervical spine? To our knowledge, most clinical reports are based on the amelioration of symptoms and radiological signs. Few clinical studies have histological studies [15]. Most histological studies are carried out in animal experiments. The biological process of bone substitutes in human cervical spine is not well documented.

In this work, the failure of cervical interbody fusions in four patients with xenograft, hydroxyapatite (HA) ceramic and β -tricalcium phosphate (β -TCP) ceramic were studied clinically, radiologically and histologically in order to reveal the biological processes of bone substitutes in the human cervical spine and to elucidate the relationship between bone ingrowth and substitute structure.

Case reports

Four patients (two men and two women) with cervical disk herniation (CDH) had undergone a discectomy and an anterior interbody fusion with HA (two cases), β -TCP (one case) and xenograft (one case) (Table 1). All these bone substitutes were commercially available in the European market [8]. The synthetic HA and β -TCP were pure components, dense without pores. Xenograft was a bovine bone. Solid cervical collars were worn after the operations. The average age of the patients was 42 years (range 30–50 years). All patients suffered from fusion failure without infection before the salvage surgery. The mean duration between the implantation and the removal of bone substitutes was 15.5 months (range 9–22 months).

Radiographs of each case were retrospectively reviewed to observe the following factors: bony bridging between the substitutes and the vertebrae; the change in height of the interventional segments; the condition of substitutes (intact/fractured/displaced); the space between the substitutes and the vertebrae. The presence of

radiolucent line or halo around bone substitutes was considered a sign of non-fusion.

The substitutes from the revision surgeries were fixed in 10% buffered formaldehyde solution and were prepared by undecalcified histological technique. All the sections were stained by van Gieson's picro-fuchsin stain. The following aspects were observed under a microscope: bone ingrowth and apposition at the bone/substitute interface; the resorption of material (the morphological changes of material and the formation of particles); inflammatory aspect.

Case 1

A 47-year-old woman with neck pain and numbness of left upper extremity underwent C5/6 discectomy and anterior interbody fusion with a dense HA. Radiographs showed that the HA was intact after surgery and cervical physiological lordosis was lost. The degenerative changes were present in C6/7: the narrowness of intervertebral space, the osteophytes, high radiological density of the adjacent endplates (Fig. 1). One month later, the symptoms appeared again (Table 2). Radiographs revealed a small anterior HA fracture and a clear space between the upper HA surface and the vertebra (radiolucent line). The HA displaced backward slightly. Six months later, the symptoms became more severe. The fracture progressed with three fragments protruding forward. Especially, the far front fragment exceeded anterior vertebral edges. At this point, the anterior half of the HA collapsed slightly and the disc spaces narrowed (Table 3). The cervical curvature changed from straight to kyphosis. Fortunately, no complication occurred. Twelve months later, a revision surgery for C5/6 fusion failure and C6/7 CDH was performed, in which the HA, the C6 vertebral body and C6/7 disk were replaced with an iliac autograft and an anterior plate. The symptoms disappeared and solid fusion was achieved 9 months later. Histological study on two large specimens with some fissures showed some small fragments around one of the specimens. No degradation particle was observed. Only a few new bones formed on the HA surface, which occupied about 5% of the total HA

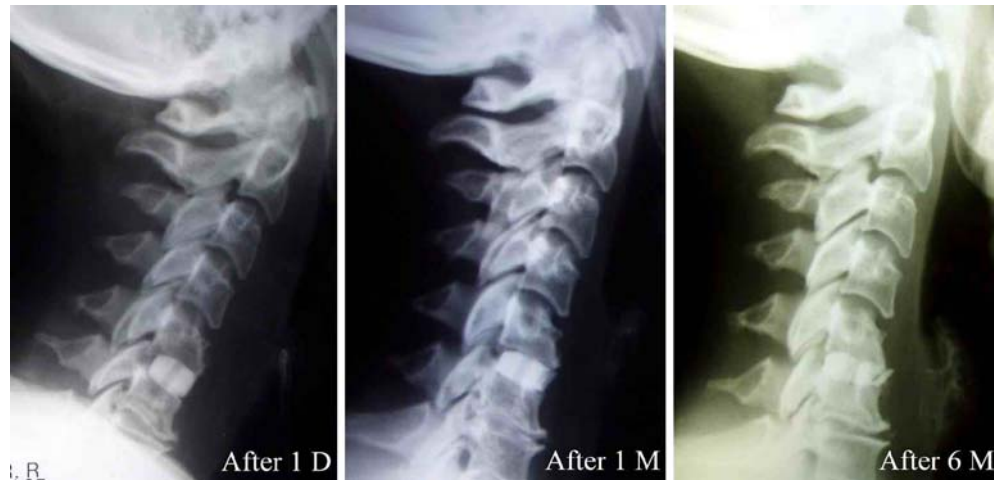
Table 1 Patient demographics

Case	Gender	Age (years)	Diagnosis	Previous operation	Salvage surgery	Retrieved materials	Interval (months)
1	F	47	C5/6 CDH	Discectomy and HA	Auto and plate	Synthetic HA	12
2	M	51	C6/7 CDH	Discectomy and HA	Auto and cage	Synthetic HA	19
3	M	30	C5/6 CDH	Discectomy and β -TCP	Auto	Synthetic β -TCP	9
4	F	40	C5/6 CDH	Discectomy and HA	1st: Xeno and plate 2nd: Auto and plate	Coral ^a Bovine bone	19 22

CDH Cervical disk herniation, HA hydroxyapatite, β -TCP β -tricalcium phosphate, Auto autograft, Xeno xenograft

^aUnavailable

Fig. 1 Case 1, cervical interbody fusion (C5/6) with dense hydroxyapatite (HA) in a 47-year-old woman. A series of lateral radiographs showed that the HA graft was intact after the operation, fractured slightly after 1 month and cracked in anterior parts after 6 months. The physiological curvature changed from straight to kyphosis gradually. The gap between the superior surface of the HA and the vertebra was clear after 1 month and obscure after the crack of the HA. The obvious degenerative changes of C6/7 intervertebral space were also observed



interface. No other tissue was determined in the other site (Table 4).

Case 2

A 51-year-old man with neck pain and numbness of right upper extremity underwent C6/7 discectomy and anterior interbody fusion with a dense HA. Radiographs showed that the HA was intact after the implantation. Two months later, the neck pain and numbness appeared again (Table 2). After 16 months, the HA fractured and sank into the adjacent vertebral bodies with one fragment displacing forward, the narrowness of intervertebral space and the slight loss of physiological lordosis. The space between the vertebrae and the implant surface was clear (Table 3, Fig. 2a). Nineteen months later, the patient underwent salvage surgery in which the HA was replaced with a cage and an autog-

enous bone. All the symptoms attenuated and solid fusion was achieved 7 months later. In the histological study, three HA samples without fissures on the surfaces were studied. One sample fractured into more than ten small fragments. Only a few new bones (occupying about 8% of the total HA interface) formed on the surface of large samples (Fig. 2b). Fibrous tissue encapsulated small fragments. A few particles were observed without obvious aseptic inflammation (Table 4). A small amount of osteoid and osteoblasts were observed on the surface of small fragments (Fig. 2c).

Table 2 The results of clinical study

Case	Bone substitute	Neck pain	Numbness of extremity	Internal fixation
1	HA	+	+	-
2	HA	+	+	-
3	β -TCP	+	-	-
4	Bovine bone	+	-	+

Case 3

A 30-year-old man underwent C5/6 discectomy and anterior interbody fusion with a dense β -TCP for neck pain and numbness of left upper extremity. The brachialgia attenuated, while the neck pain sustained after operation (Table 2). Radiographs revealed that the β -TCP was intact without fracture, 4 and 8 months after operation. No bony bridging was observed. The cervical lordosis reduced without the loss of disc space. The gap between the vertebrae and the implant surface was clearer after 8 months than after 4 months (Table 3, Fig. 3a). Nine months later, the patient underwent revision surgery during which β -TCP was replaced with

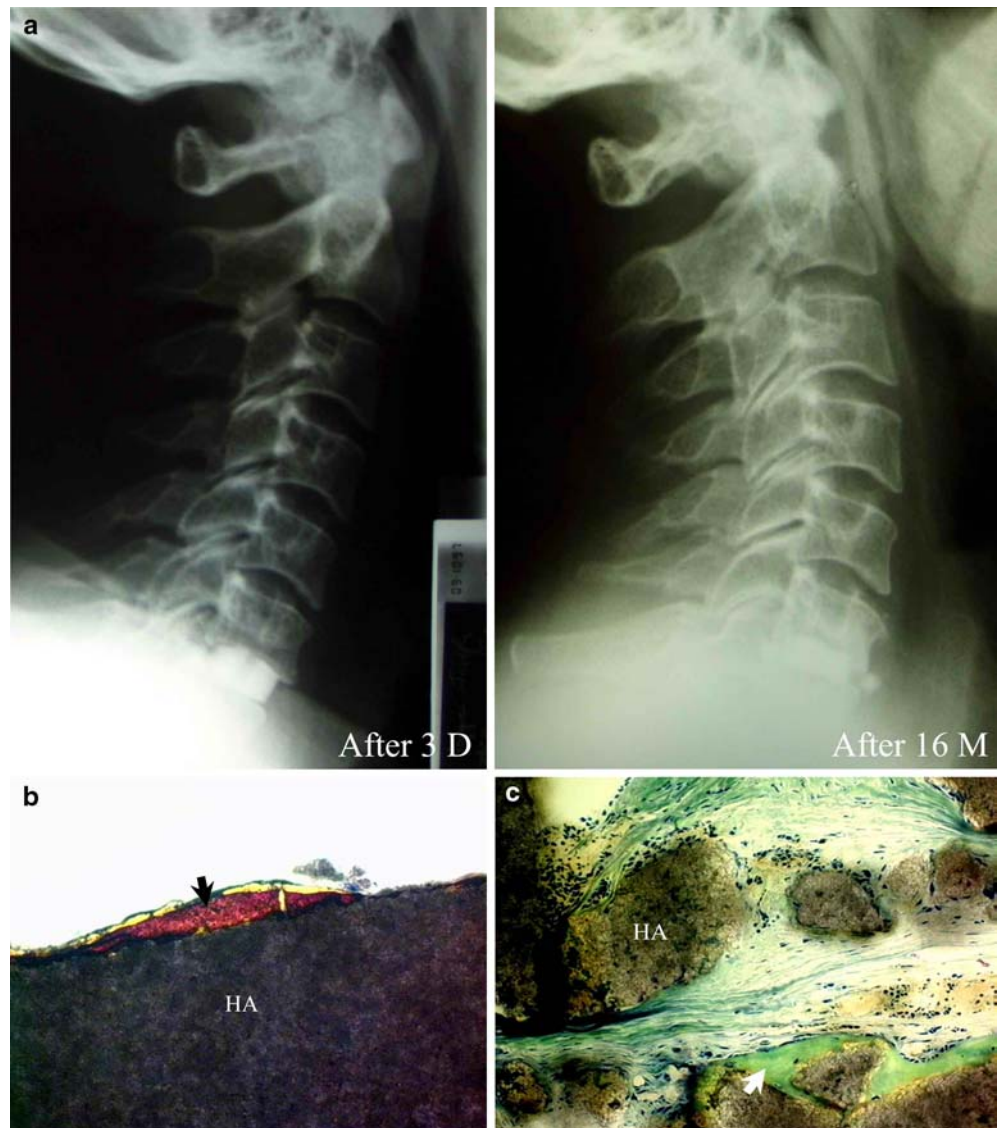
Table 3 The results of radiological study

Case	Bone substitute	Height of disc space	Condition of graft	Lucent line
1	HA	Narrow anteriorly	Fractured	+
2	HA	Narrow	Fractured	+
3	β -TCP	No change	Intact	+
4	Bovine bone	No change	Intact	+

Table 4 The results of histological study

Case	Bone substitute	Ingrowth	Interface apposition	Particles	Aseptic inflammation
1	HA	-	Bone	-	-
2	HA	-	Bone/fibrous tissue	+	-
3	β -TCP	-	Bone	+	+
4	Bovine bone	Fibrous tissue	Fibrous tissue	-	-

Fig. 2 Case 2, cervical interbody fusion (C6/7) with dense hydroxyapatite (HA) in a 51-year-old man. **a** Lateral radiographs showed that the HA fractured and sank into the vertebrae with the narrowing of intervertebral space 16 months after the surgery. A small fragment displaced forward and exceeded the anterior rim of the adjacent vertebrae. The gaps between the vertebrae and the HA were clear. **b** Microscopic examination showed only a few new bones (*arrows*) on the surface of the large HA. (van Gieson's picro-fuchsin stain; original magnification $\times 25$). **c** Microscopic examination of several HA fragments showed that the fragments were encapsulated by fibrous tissue. A few osteoids (*arrows*) were present on the surface of the fragments with osteoblasts. (van Gieson's picro-fuchsin stain; original magnification $\times 50$)



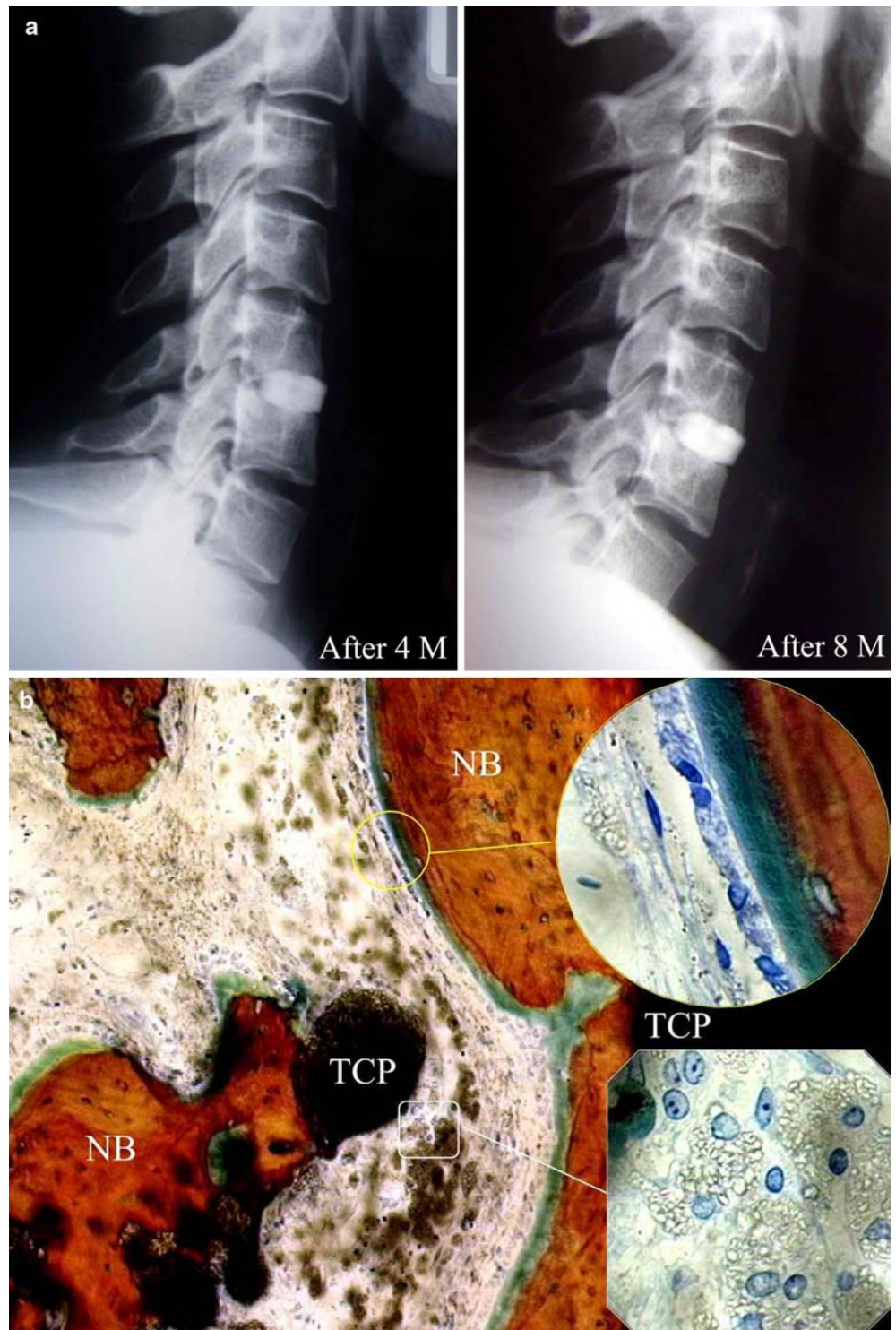
an iliac autograft. The neck pain disappeared and fusion was achieved 5 months later. Histological study on the β -TCP sample showed no fissure on the surface, but some fragments and numerous degradation particles presented around the β -TCP. New bones encapsulated the fragments partially or completely. The particles were phagocytosed actively by numerous macrophages. There were more new bones with active osteoblasts (occupying about 15% of the total β -TCP interface) on the β -TCP surface than on the HA surfaces of case 1 and case 2 (Table 4, Fig. 3b).

Case 4

A woman, 40 years old, underwent the C5/6 discectomy and anterior interbody fusion with a coral for neck

pain and numbness of right upper extremity. But the neck pain existed persistently. After 19 months, the coral was replaced with a bovine bone and an anterior plate. Unfortunately, the neck pain sustained after operation (Table 2). Radiographs showed that bovine bone was intact without displacement 20 months after operation. The space between the implant and the vertebrae was clearer 20 months than 5 days after operation except that the gap between the inferior graft surface and the vertebra disappeared. The height of intervertebral space was well preserved, while the physiological lordosis was lost (Table 3, Fig. 4a). Twenty-two months after the second operation fusion failure was established, the xenograft was replaced with an iliac autograft and an anterior plate. The symptoms disappeared and fusion was achieved 4 months after operation. The first graft could not be made available.

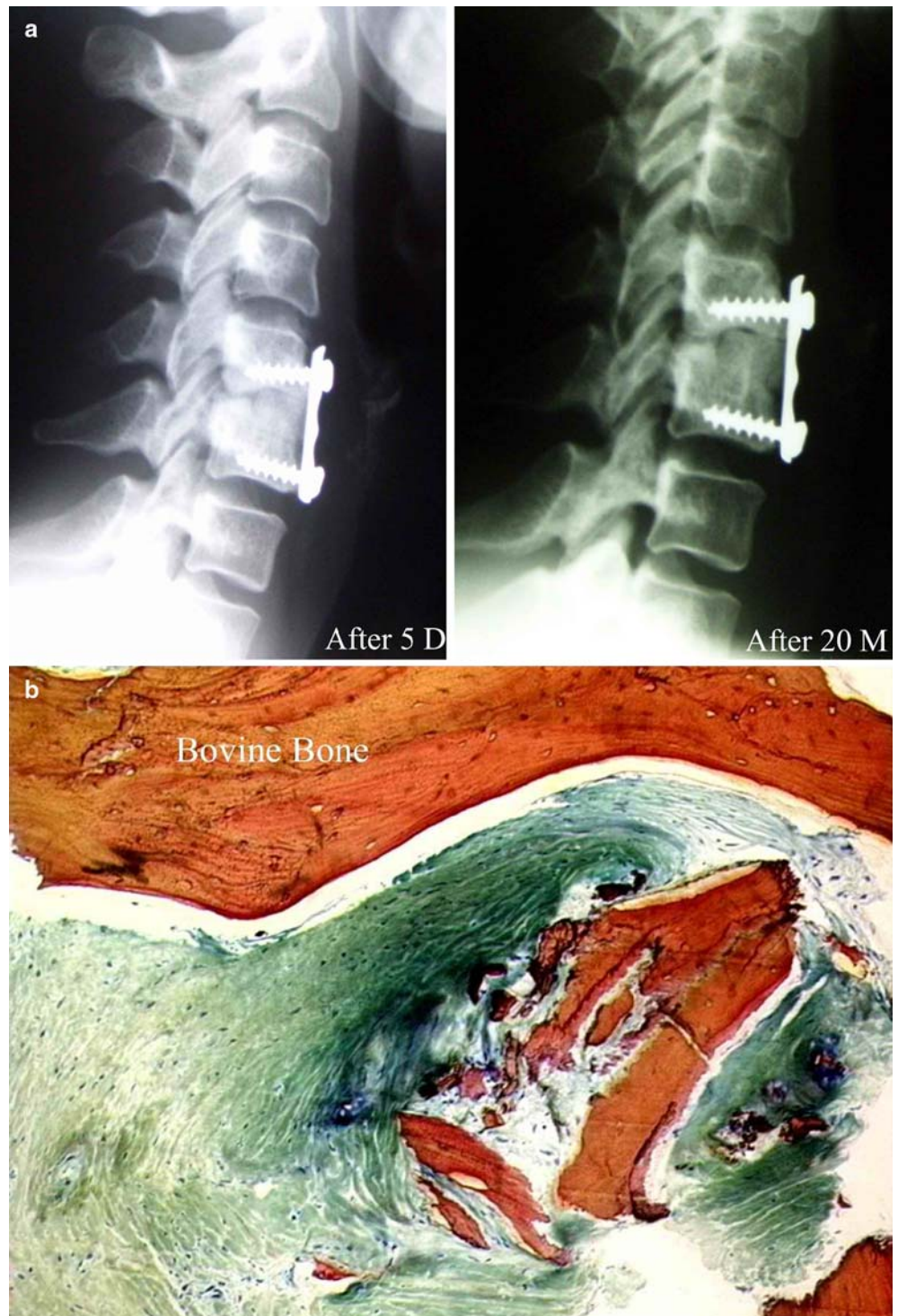
Fig. 3 Case 3, cervical interbody fusion (C5/6) with dense β -TCP in a 30-year-old man. **a** Lateral radiographs showed that radiolucent line around the β -TCP, which was clearer 8 months after surgery than 4 months after surgery. **b** Microscopic examination showed new bone formation (NB) on the surface of the large β -TCP and its fragments with active lined osteoblasts (round window). Numerous degradation particles presented around the β -TCP, some of which were phagocytosed by the macrophages (hexagonal window). (van Gieson's picro-fuchsine stain; original magnification $\times 25$; round and hexagonal windows, original magnification $\times 100$)



The second xenograft was studied. Histological observation showed that dense fibrous tissue encapsulated the bovine bone. The intertrabecular space was filled with fibrous tissue with clear gap between fibrous tissue

and the bovine scaffold. Some parts of bovine bone were necrotic and fragmental. Neither degradation particle nor macrophage was observed (Table 4, Fig. 4b).

Fig. 4 Case 4, second cervical interbody fusion (C5/6) with bovine bone and a plate in a 40-year-old woman. **a** Lateral radiographs showed that the gap between the superior surface of bovine bone and the vertebra was larger 20 months after the surgery than 5 days after the implantation, while the gap between the inferior surface and the vertebra disappeared 20 months after the implantation. **b** Microscopic examination showed that bovine bone was encapsulated by dense fibrous tissue with aspects of necrosis. No degradation particle or inflammatory reaction was observed. The gap between the bovine bone and fibrous tissue was clear. (van Gieson's picro-fuchsine stain; original magnification $\times 25$)



Discussion

In this work, two kinds of nonautologous materials, xenograft and C-P ceramics, were used for cervical interbody fusion. The ideal nonautologous material

should be biocompatible and provide instant mechanical resistance to maintain physiological lordosis, intervertebral and foraminal height. Moreover, it would induce a rapid and complete fusion without pain. Both kinds of materials satisfy only part of these requirements.

Xenograft is mainly derived from bovine bone. The radiographs of this case showed partial fusion of bovine bone and the vertebra which could not be proved in the histological study. Moreover, the patient experienced severe neck pain. These results did not coincide with previous reports, in which satisfied clinical results and stable cervical segments were achieved despite fibrous fusion in anterior cervical spine with bovine bone [18, 23]. Although a plate was employed in this case, which provided immediate instability, and bovine bone had a similar structure as human cancellous bone, the fusion failure still occurred. The reason lay in the low biocompatibility of bovine bone, which was revealed in the histological study (the gap between the bovine scaffold and fibrous tissue). Furthermore, there was the potential for virus transmission. Thus, one should be careful when bovine bone is chosen for anterior cervical fusion.

Hydroxyapatite and β -TCP are two kinds of biocompatible C-P ceramics. HA is difficult to degrade and the bone/HA bond is ascribed to the biologic apatite microcrystals on the surface [5, 10, 16]. However, β -TCP is more soluble and bone ingrowth is at the expense of the ceramic [6]. This study documented these different biological processes in human cervical spine. In the section of β -TCP a strong cell-mediated degradation and a faster bioabsorption were observed, while only in one of the HA samples there were a few degradation particles without macrophage, which indicated its stability. Moreover, new bones were fewer at the interface of HA than that of β -TCP. These results suggested that the biodegradation and bone regeneration in the cervical spine were better in the β -TCP than in the HA, which coincided with the results of the previous animal study [13].

All the C-P ceramics in this study were dense, which provided only the limited exterior surface. Lack of macropores in the material reduced the surface for new bone colonization. The dense ceramic in this study acted only as a spacer. New bone/substitute bond happened both in porous and dense HA [10, 25] and new bone formation was at the expense of the β -TCP [6], so the total potential surface for bone ingrowth played a role in the new bone colonization process. High incorporation rate and good clinical results have been reported in anterior cervical interbody fusion with porous coralline

HA [22, 24], which implied that the porous ceramic could act as a scaffold to support bone ingrowth. But the size of the pores and interconnections has the effect on the bone ingrowth. HA with 500 μm pores had stronger osteogenesis than that with 200 μm [12] and the interconnection size over 50 μm could assure mineralised bone formation [14]. A 130 μm mean interconnection size and a 175–260 μm pore diameter size led to the best osteoconduction result in the ceramic centre [7]. Thus, the porous ceramics with well-controlled pores and interconnections could be chosen for cervical interbody fusion.

In this study, the HA and β -TCP were dense, but all of them were fractured, which was revealed by radiographs or histological sections. These major or minor fractures could be yielded by either the violent manoeuvres during the intervention or the segmental micromotion after operation because of the lack of reliable fixation. The dense HA blocks were superior in maintaining disc space height [2, 4, 17]. But both dense [2] and porous HA [9, 22] fractured, even leading to spinal cord compression. The incidence of HA dislodgement or fracture was 6% [19]. On the one hand, the more dense the ceramic, the lesser the number of fractures and the related fusion failure that would happen. On the other hand, the porous structure favoured bone ingrowth and assured solid fusion. How to balance these two factors in order to achieve optimal C-P ceramic for cervical spinal interbody fusion? Firstly, the macrostructure could be further optimised to mimic the natural bone. The central part of C-P ceramic is porous, bioabsorbable material like cancellous bone and the peripheral part is dense like the cortical bone. Secondly, biphasic C-P ceramic (the combination of HA and β -TCP) could be chosen as the material, which provides faster bioabsorption than pure HA and stronger mechanical property than pure β -TCP [10, 20].

The biological processes of xenograft and C-P ceramics in human cervical spine were elucidated through four clinically failed interbody fusion cases. The composition and the structure of the C-P ceramics could be refined further. The complications of these materials in the cervical spinal fusion should be highlighted. This study has only a few cases. Further study on more cases is necessary in the future.

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