Multiple Giant Cell Tumors in Maxilla and Skull Complicating Paget's Disease of Bone

Kazunari KARAKIDA[*1], Yoshihide OTA[*2], Takayuki AOKI[*2], Tadashi AKAMATSU[*3], Hiroshi KAJIWARA[*4] and Kenichi HIRABAYASHI[*4]

[*1]*Department of Oral and Maxillofacial Surgery, Tokai University Hachioji Hospital*
[*2]*Department of Oral and Maxillofacial Surgery, Tokai University School of Medicine*
[*3]*Department of Plastic Surgery, Tokai University School of Medicine*
[*4]*Department of Pathology, Tokai University School of Medicine*

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Paget's disease of bone (PDB) is a very rare disease in the Asian countries including Japan, although as a bone metabolism disease it is relatively common in Europeans and Americans. An infrequent complication of PDB is the giant cell tumor (GCT).
We encountered a case of GCT in the maxilla complicating PDB in a 57-year-old Japanese woman. She developed her first GCT in the right occipital bone 14 years ago, which was resected. At the same time, she was given a diagnosis of polyostotic PDB. Four years ago, she developed two GCTs in the parietal bone, which were resected. Recently, she was found to have a GCT in the maxilla and maxillotomy was performed. The sporadic form of GCT associated with PDB almost always arises in pagetic bone. The clinicopathologic features of this rare lesion are described and correlated with a review of the literature.

Key words: Giant cell tumor, Paget's disease of bone, Maxilla, Skull

INTRODUCTION

Paget's disease of bone (PDB) is a very rare disease in the Asian countries including Japan, although as a bone metabolism disease it is relatively common in Europeans and Americans. The cause of PDB is incompletely understood, but genetic factors have clearly an important role as roughly, 15% of patients have a positive family history and geographic clustering.

The long-term evolution of PDB increases the risk of developing an osteosarcoma, malignant fibrous histiocytoma, fibrosarcoma and chondrosarcoma in pagetic bone. The prevalence has been estimated to be 1% in patients with PDB [1]. In contrast, giant cell tumor (GCT) is a very rare complication of PDB [2–11].

GCTs associated with PDB have features distinct from conventional GCTs. GCTs complicating PDB occur in the regions affected by PDB, such as the skull and facial bones, while conventional GCTs arise most commonly in long bones, especially in the area of the knee joint [12]. GCTs associated with PDB occur in older individuals while conventional GCTs typically develop in relatively young individuals aged 20 to 40 years. Most cases of GCT complicating PDB occur with polyostotic or, sometimes multiple involvements [13].

We present a case of multiple GCTs in maxilla and skull complicating PDB and compare the clinicopathologic features with those reported in the literature.

CASE REPORT

A 57-year-old Japanese woman was referred to Department of Oral and Maxillofacial Surgery, Tokai University Hospital, presenting with a painless, slow growing left maxilla mass that had been present for 3 months.

Fourteen years earlier she underwent an excision of a GCT in the occipital bone that was histopathologically confirmed to be affected by PDB by the department of neurosurgery, Tokai University Hospital. The GCT had destroyed the lamina externa and invaded the diploe of the bone (Fig. 1a). The results of the examination revealed that the facial bone, lumber vertebrae, sacrum, and pelvis, as well as the skull, were affected by PDB, and polyostotic PDB was diagnosed (Fig. 1b and 1c). Four years ago she experienced 2 GCTs in the parietal bone that were resected (Fig. 1d). Her family history had no remarkable findings and was negative for PDB.

On physical examination a 45 × 47 mm painless large mass across the center in the left maxilla was found. The tumor surface was smooth with focal granulation-like proliferation and redness. Several teeth were involved and displaced in the tumor mass (Fig. 2a). MRI scans of the left maxillary mass showed the expansive growth from the maxilla through the maxillary sinus, and iso signal intensity to muscle on T1-weighted image (Fig. 2b). MRI scans after gadolinium administration provided patchy speckled

Kazunari KARAKIDA, Department of Oral and Maxillofacial Surgery, Tokai University Hachioji Hospital, 1838 Ishikawa, Hachioji-city, Tokyo 192-0032, Japan. Tel: +81-426-39-1111 Fax: +81-426-39-1144 E-mail: karakida@is.icc.u-tokai.ac.jp

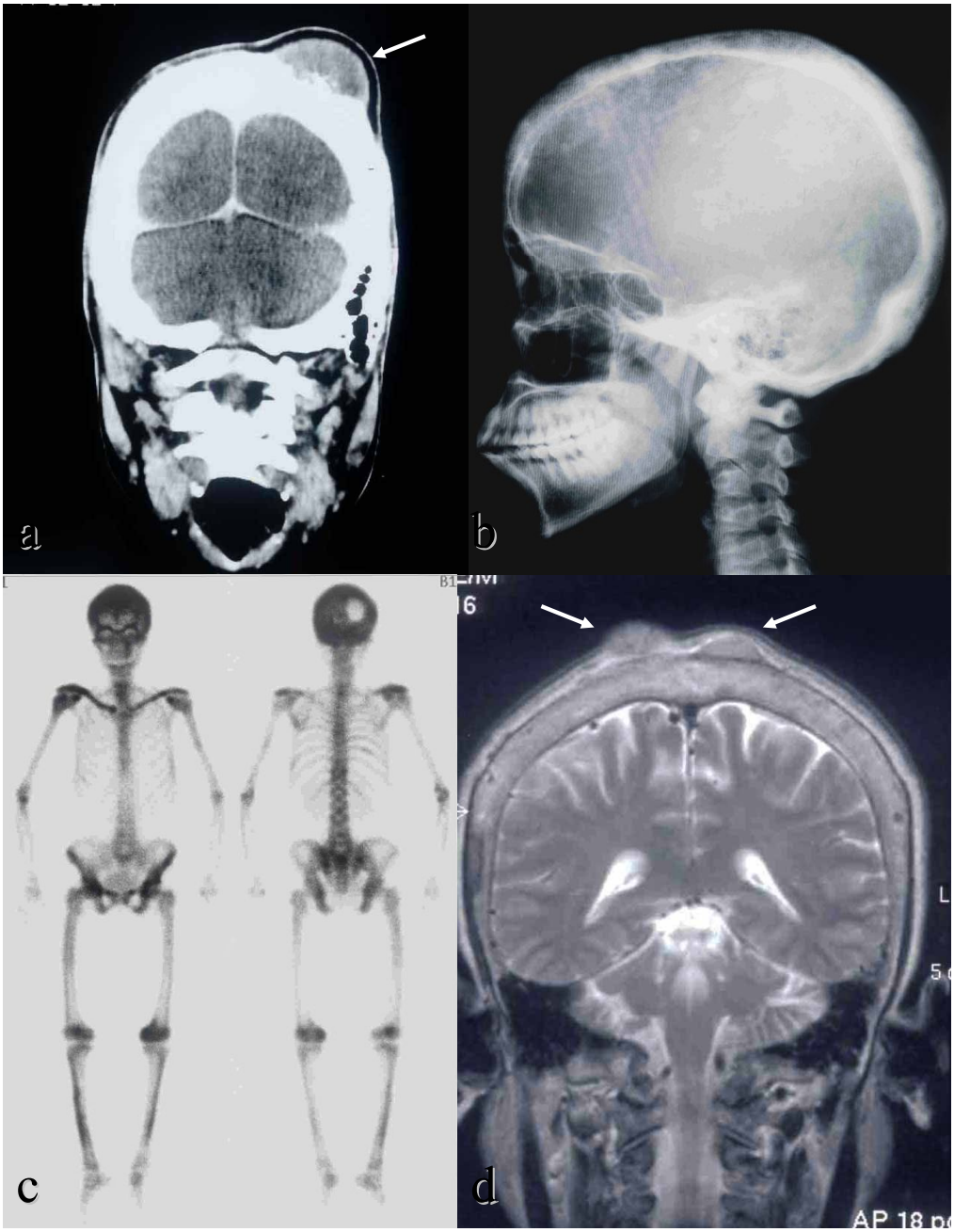

Fig. 1 a) Coronal soft tissue window computed tomography scan images shows giant cell tumor of the left occipital bone affected with paget's disease of bone seen at the first visit (allow).
b) Skull X-ray, Lateral view, showing a cotton-wool-like appearance in the frontoparietal regions.
c) Anterior (left) and posterior (right) views technetium-99m-labeled diphosphonate bone scintigraphy showing in the skull, pelvis, sacrum, and lumbar spine of increased uptake.
d) Coronal T1-weghted MR images of Giant cell tumors of the parietal bone affected with paget's disease of bone seen at the second visit (allow).

enhancement in the mass lesion (Fig. 2c). Her urinary deoxypyridoline, serum calcium and other laboratory data were within normal range except the elevation of alkaline phosphatase level (1,634 IU/L.; normal range, 100–310 IU/L). GCT was histopathologically diagnosed based on the results of biopsy.

Because radiography imaging scans predicted that the tumor was a hypervascular mass, carotid angiography with tumor artery embolization of the left maxillary artery that was the main feeder artery was performed as pre-operative therapy. One week later, maxillotomy and immediate reconstruction were accomplished using a rectus abdominis musculocutaneous flap, with the patient under general anesthesia.

Microscopic evaluation of the surgical specimen revealed proliferation of large osteoclast-like giant cells and uniform ovoid mononuclear cells. The tumor cells possessed 1 or 2 small nucleoli. Atypical mitoses were not found. These features were consistent with the diagnosis of GCT. The maxilla surrounding the

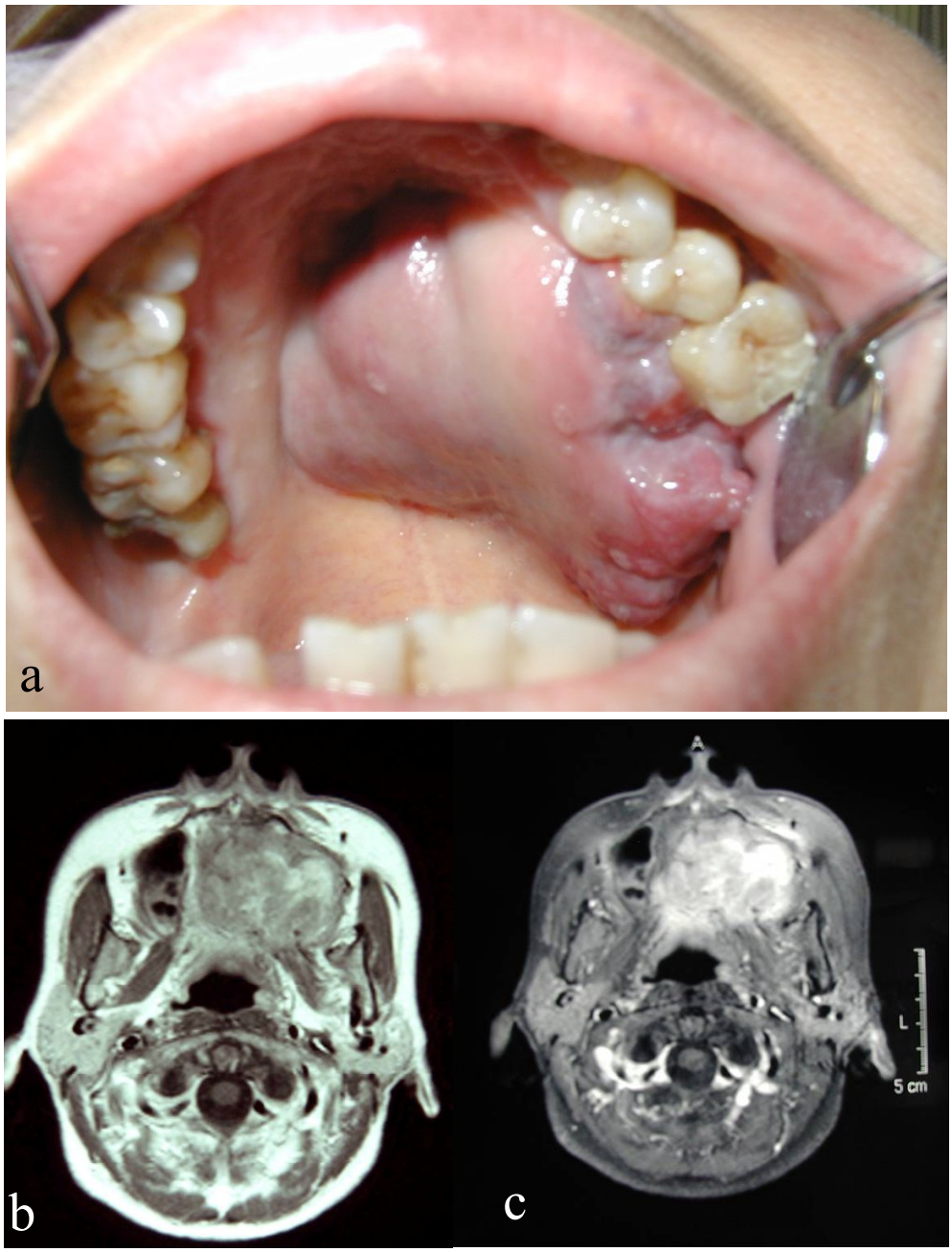

Fig 2 a) Photograph shows a maxillary lesion expanded by the tumor mass that has included teeth.
b) Axial T1-weighted MR imaging.
c) Gadolinium-enhanced T1-weighted magnetic resonance imaging showing patchy speckled enhancement in the lesion mass.

tumor revealed increased numbers of osteoclasts and osteoblasts. Multiple osteoclastic giant cells were noted. Fibrous change was noted in the bone marrow. A polarized photomicrograph shows multiple cement lines and the disorganized or mosaic pattern in cortical bone . These features were consistent with the diagnosis of PBD (Fig. 3a–d).

There was no evidence of recurrence or metastasis 1 year and 3 months after the initial surgery, but the patient died of other disease.

DISCUSSION

PDB is a condition characterized by abnormal and anarchic resorption and deposition of bone, resulting in distortion and weakening of the affected bones. The prevalence of PDB varies racially and geographically. In Europe and the United States, PDB is the most common metabolic disease after osteoporosis and approximately 3% to 4% of the population over 40 years old have this disease [13]. In Asian countries including Japan, PDB is an extremely rare disease. The Japan National Survey conducted in 2003 identified only 169 cases of PDB. The incidence of PDB in Japan is 0.15 cases per 100,000 general population, and 0.41 cases per 100,000 population over 55 years old [14].

PDB is complicated by fracture and osteoarthritis, and infrequently, malignant neoplasm. Osteosarcoma is the most common malignant neoplasm complicat-

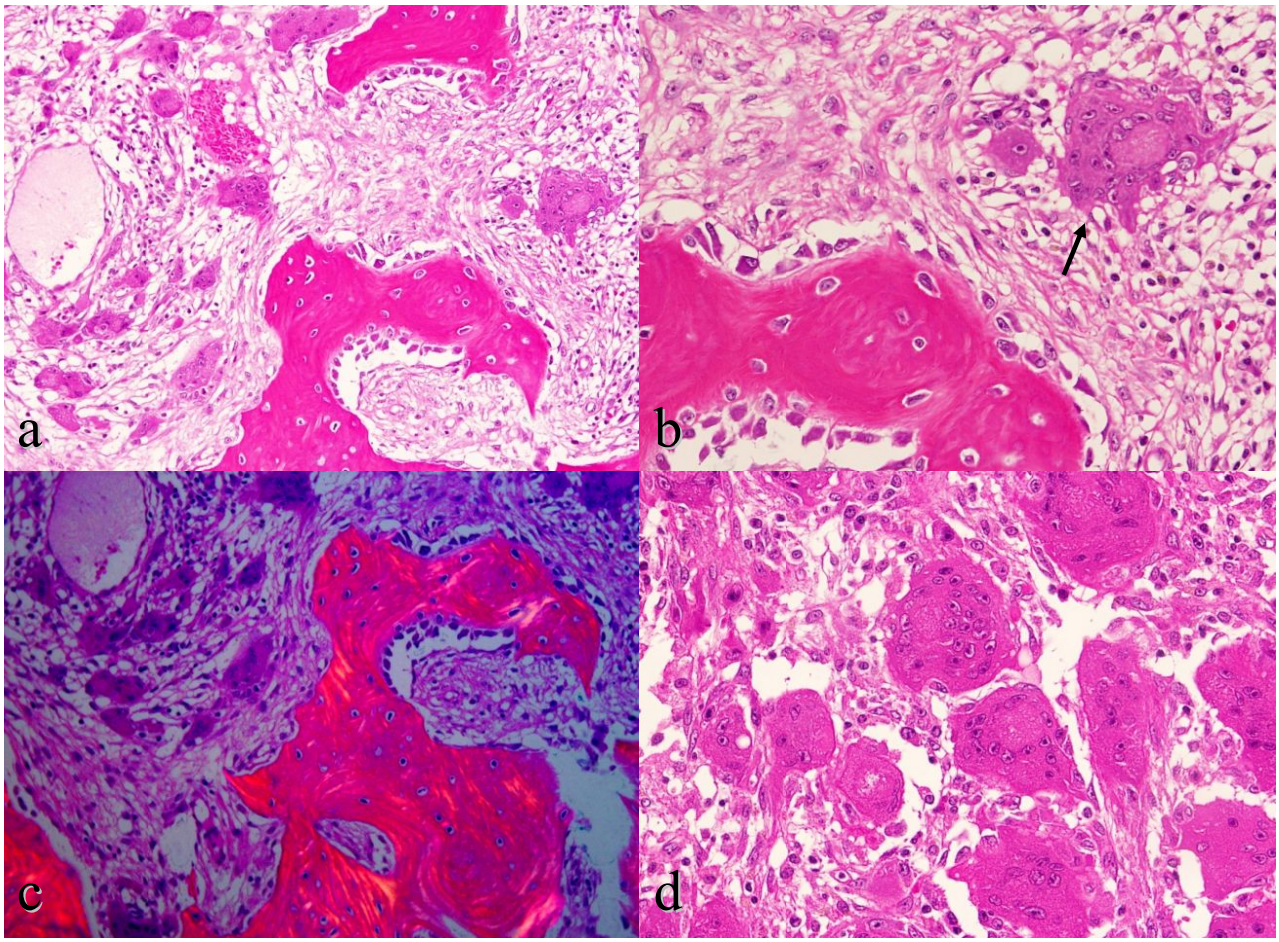

Fig. 3 Active phase of Paget's disease (a, b, c).
a) Photomicrograph reveals increase of osteoclasts and osteoblasts (×100 original magnification).
b) Multiple osteoclastic giant cells are noted (arrow). Fibrous change noted in the bone marrow (×200 original magnification).
c) Polarized photomicrograph shows multiple cement lines and the disorganized or mosaic pattern in cortical bone (×150 original magnification).
Giant cell tumor
d) proliferation of large osteoclast like giant cells and uniform ovoid mononuclear cells are seen. (×200 original magnification).

ing PDB, with an incidence of approximately 1% [1]. The occurrence of benign GCT in association with PDB has been reported, but it is extremely rare as compared with the occurrence of osteosarcoma [2–11]. According to the study by Dahlin *et al.* only 1 of 407 patients with PDB experienced GCT [15]. In Asian countries including Japan, there have been no reports of a case of GCT associated with PDB.

Different types of giant cell lesions, such as aneurismal bone cyst, cherubism, brown tumors of hyperparathyroidism, and giant cell reparative granuloma (GCRG) can commonly affect the maxilla. In these lesions, differential diagnosis with GCRG is problematic. Typical cases of GCRG differ from GCT, as giant cells are smaller and organized in clusters, and stroma is more fibrotic, sometimes showing focal hemorrhage or hemosiderin deposits. Whereas in true GCTs are randomly scattered throughout the tumor [12].

The mechanism whereby GCT occurs in association with PDB has not been elucidated. In our patient, however, some relationships that were unlikely to be coincidental between PDB and multiple GCTs were noticed. Conventional GCTs commonly affect the epimetaphyseal locations of long bones, but infrequently the skull or maxillo-facial bone, while the GCTs developing in our patient involved the skull and maxillo-facial bone, which were consistent with the most common sites affected by PDB. This patient developed her first GCT in the right occipital bone at the age of 43, two GCTs in the parietal bone at the age of 53, and another GCT in the maxilla at the age of 57, unlike conventional GCT that commonly occurs in individuals aged 20 to 30 years [12]. The patient suffered from polyostotic PDB and all of her multiple GCTs involved the bones that were affected by PDB. These findings were consistent with the characteristics of GCT associated with PDB (Table).

Although this patient experienced GCT repeatedly, the possibility of the recurrence of the disease may be ruled out. Treatment of GCT generally involves curettage and resection. The local recurrence rate after curettage alone is high at 15.5% to 42% [16]. When the complete resection of GCT was accomplished, however, the risk of local recurrence is reduced and the prognosis is good. All the GCTs invading the skull in our patient were resected with an adequate margin at the

Table Clinical features of 18 cases of giant cell tumors complicating Paget's disease of bone

Case no.	Year	authors	Gender	Age (yr)	Geographical area	Consanguinity	GCT location	PDB type
1	1979	Jacobs *et al.* [2]	F	59	Italy	Yes	Skull	-
2			F	62	Italy	Yes	Maxilla, Skull	Poly
3			M	59	Italy	Yes	Vertebra	Poly
4			M	57	Italy	Yes	Lumbar and Sacrum vertebrae	Poly
5			F	46	Italy	Yes	Skull -	
6	1982	Mirra and Gold *et al.* [3]	M	56	United States	-	Femur	Poly
7	1991	Potter *et al.* [4]	F	58	United States	-	Spinal canal, Vertebra, Pelvis	Poly
8			M	65	United States	Yes	Poly Paraspinal, Ilium, Skull, Mandible	Poly
9			F	58	United States	Yes	Ilium, Spine	Poly
10			M	54	United States	Yes	Scapula, Spine	Poly
11	1992	Bhambhani *et al.* [5]	M	52	Italy	No	Mandible, Vertebra	Poly
12	1995	Dixon *et al.* [6]	F	85	United Kingdom	-	Femur	Poly
13	1999	Pathak *et al.* [7]	M	73	United States	-	Ilium, Pelvis	Poly
14	2003	Mooney *et al.* [8]	M	73	Australia	-	Maxilla	Poly
15	2007	Hock *et al.* [9]	M	62	United States	No	Femur	Mono
16	2007	Campidelli *et al.* [10]	M	53	Italy	-	Scapular, Mandibular, Orbita	Poly
17	2009	Nuzzo *et al.* [11]	M	68	Italy	Yes	Pelvis	Poly
18	2010	Karakida *et al.*	F	57	Japan	No	Maxilla, Skull	Poly

Poly: polyostotic type, Mono: monostotic type

department of neurosurgery, Tokai University Hospital. Because her GCTs were metachronous and affected distant regions (the occipital bone, parietal bone, and maxilla), it is very unlikely that she experienced a local recurrence of the diseases. Therefore, this case was considered to be the metachronous occurrences of independent GCTs invading the bones that were affected by PDB.

In recent years, recurrent mutations in genes have been discovered as a cause of PDB or related syndromes. This gene has been implicated in the signaling cascade involving RANK, which is essential to osteoclastogenesis. It is reasonable to postulate that such abnormal osteoclastogenesis could produce a GCT of PDB [9].

The current first-line treatment for patients with PDB consists of a bisphosphonate to inhibit bone resorption [1]. Bisphosphonate has recently attracted attention also as an adjunct therapy for patients with GCT. Tse *et al.* [17] reported that treatment with bisphosphonate significantly reduced the recurrence rate of the disease in patients with GCT who received operative therapy. Bisphosphonate is considered to suppress the expression of RANKL and reduce the growth and activity of osteoclasts. This mechanism of bisphosphonate is common to PDB and GCT, which may indicate the close association between these diseases.

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