in vivo *20*: 665-670 (2006)

Osteoblastoma of the Jaw: Report of Two Cases and Review of the Literature

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Abstract. *Osteoblastoma is a benign bone tumor of osteoblastic origin. Two cases, an 8-year-old boy and a 24-year-old man, are presented. Both tumors were resected with wide surgical margins and neither patient had adjuvant radiation or chemotherapy. The patients showed no evidence of local recurrence after six to seven years. The clinical, radiological, histological and immunohistochemical features are described. Differential diagnosis and immunohistochemical features potentially useful for refining diagnosis of osteoblastoma are also discussed.*

Osteoblastoma is a benign neoplasm of the bone, accounting for approximately 1% of all primary bone neoplasms, with an m/f ratio of 2:1 (1-6). It usually occurs in young adults, with a mean age of 20 years and primarily involves the vertebral column, long bones, small bones of hands and feet (metacarpal and metatarsal) and facial bones including the jaw. To date, 71 cases of osteoblastoma of the jaw have been reported, including our cases (7, 13, 14).

Osteoblastomas may be classified into cortical, medullary and periosteal types (8) Histologically, they are tumors of osteoblastic origin, characterized by a proliferation of osteoblasts and production of osteoid within a highly vascular fibrocellular stroma. Variable amounts of calcification occur and multinucleated giant cells, presumably osteoclasts, are often present. The clinical symptoms are non-specific, but pain, local tenderness and swelling are usually reported. The duration of pain varies from a few months to several years and may be relieved by salicylates, as is the case with osteoid osteoma (9-11).

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Key Words: Osteoblastoma, MIB1, p53, apoptosis, mandible.

Most lesions reported in the literature were treated by curettage, local excision and surgical for complete removal of the tumor. There is no agreement regarding the use of post-operative radiotherapy, since there is a risk of inducing more aggressive behavior (12).

Two cases of osteoblastoma of the jaw, together with clinical, radiological, histopathological and immunohistochemical findings, are presented. The histopathological differential diagnosis, and immunohistochemical features potentially useful for refining this tumor are discussed.

Case Reports

Case 1. The patient, an 8-year-old boy, was referred to the Maxillofacial Surgery Department of the Stomatological Institute, Milan, with a swelling in the posterior right maxilla. Intra-oral examination revealed a bony-hard swelling and multiple missing teeth in the right maxillary molar area.

Panoramic radiography showed a mixed pattern of radiolucency and radiopacity from the first permanent molar to the maxillary deciduous canine, measuring 1.5 cm and bilateral hypodontia of the maxillary and mandibular permanent teeth (Figure 1A). An incisional biopsy was taken and a diagnosis of osteoblastoma was rendered. The patient underwent right maxillectomy with reconstruction of the defect; he had no adjuvant radio- or chemotherapy. There is no evidence of recurrence seven years after surgery.

Case 2. A 24-year-old man complained of a painless slow-growing mass on the left side of the mandible, first noted approximately 1 year earlier. Medical examination was non-contributory, and there was no history of trauma. Intra-oral examination showed a swelling approximately 1 cm in diameter on the left side of the mandible. At palpation, the mass was bony-hard and non-tender. The overlying skin was normal in color, consistency and temperature and there was no motor or sensory deficit. Intra-oral examination revealed

Table I. *Immunohistochemical findings.*

Antibody	Supplier	Dilution	Reactivity Case 1	Reactivity Case 2	Antigen retrieval
MIB-1	DAKO	1:100	+	++	Tris-EDTA Twin 20
Apoptosis	Kit ROCHE	Prediluted	++	+	nonr
Factor VIII	DAKO	1:500	++	+ +	Tryspin 37° / 20 min
p53	NOVOCASTRA	1:200	++	+	Tris-EDTA Twin 20

+focally-positive for a limited number of cells; ++ focally or diffusely-positive for numerous cells.

normal dentition and occlusion with expansion of the buccal cortex and lingual cortical plate. Radiographic examination of the jaws showed a poorly-defined, "ground-glass" radiopaque lesion in the posterior body of the mandible. An incisional biopsy was taken and a diagnosis of osteoblastoma was rendered. The patient then underwent left mandibulectomy and reconstruction of the surgical defect. There has been no recurrence after six years.

Materials and Methods

The excised biopsy tumor specimens were fixed in 10% formalin-buffered and paraffin embedded. Sections of 5 μ were stained with hematoxylin-eosin, hematoxylin-van Gieson, and PAS-hematoxylin. For immunohistochemistry, the avidin-biotin complex (ABC) method was applied. Sections were deparaffinized with xylene for 15 min before rehydration through graded alcohols to water. Antigen retrieval was performed on the slides by placing them in a bath of 10 mM citric acid pH 6 and boiling for 16 min using an autoclave. A panel of monoclonal antibodies was used for the following markers (Table I): Factor VIII (DAKO 1:500), Ki67 antigen (MIB-1, 1:100 DAKO), p53 (NOVOCASTRA 1:200 antibodies) and apoptosis (Kit ROCHE pre-diluted). Of the above antibodies, MIB-1 and p53 sections were treated at 95°C for 15 min in TRIS EDTA TWIN 20 solution. The immunohistochemical antibodies, their sources, and dilutions are listed in Table I. Appropriate controls were tested simultaneously. The immunohistochemical reactivity was evaluated and graded as follows: – (negative), no staining; + (positive), focally positive for a limited number of cells; and ++ (intensely positive), focally or diffusely positive for numerous cells.

Results

The microscopic examination of Case 1 revealed that the lesion was composed of irregular sheets and strands of osteoid and calcified bone rimmed by single layers of osteoblasts. The osteoblasts had large, hyperchromatic nuclei and eosinophilic cytoplasm. Scattered large osteoclast-type giant cells within the stroma, which was loose and fibrovascular, were noted (Figure 1B).

The histological examination of decalcified sections of Case 2 revealed a thin layer of irregular osteoid, bone and cement within a fibrovascular stroma consisting of hypercellular fibrous connective tissue containing scattered irregular foci of osteoid matrix and thin trabeculae of woven bone; some of this woven bone showed osteoblastic rimming (Figure 2B).

The results of the immunohistochemical staining are provided in Table I. Immunohistochemical reactivity for factor VIII was detected (Figures 1C and 2B) and both cases were positive. Different reactivities for apoptosis and proliferation index were observed. Focally positive immunoreactivity for MIB-1 was observed in Case 1, which was also intensely positive for apoptosis and p53 (Figures 1D, E and F). Case 2 was characterized by intense reactivity for MIB-1, focal positivity for p53 and for apoptosis (Figures 2C, E and D).

Discussion

We report two cases of benign osteoblastoma of the jaw originating in the medullary spaces. To date, a total of 71 cases of osteoblastoma of the jaws has been reported including our cases (7, 13, 14).

Conventional osteoblastomas are biologically benign with limited growth potential and typically do not exceed 4 cm in diameter (5). However, there is a small subgroup of borderline osteoblastomas that possesses a locally-aggressive growth pattern, usually exceeding 4 cm (5, 15) These tumors cannot easily be classified as "conventional" osteoblastomas or osteosarcomas (8) and have, thus, been separated from the classic lesion and designated as osteoblastoma-like osteosarcoma and malignant osteoblastomas or aggressive osteoblastomas (5, 15-19).

Histologically and clinically, differential diagnosis for osteoblastoma ranges from a variety of benign and malignant tumors, ranging from cementoblastoma, osteoid osteoma, fibrous dysplasia, to borderline forms of the above malignancies, up to low-grade osteosarcoma.

Cementoblastoma is histologically similar to osteoblastoma, but differs in its histogenesis and site predilection; current evidence suggests that, unlike osteoblastoma, cementoblastoma is an odontogenic tumor (20). In cementoblastoma, the neoplastic tissue is characteristically fused with the cementum and dentin of the apical third of the tooth root, whereas osteoblastoma does not exhibit such a relationship; in our cases

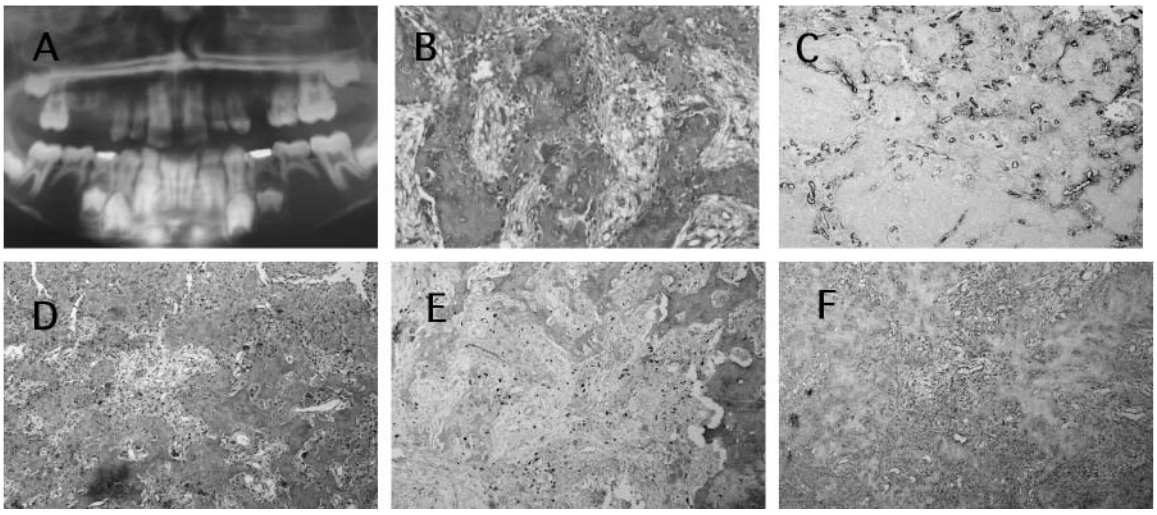

Figure 1. *Case 1. A: Panoramic radiograph showing a unilocular radiolucency between roots of right canine and the first molar. B: Microscopic view shows typical features of osteoblastoma, with osteoblastic rimming of calcified bone The connective tissue is characterized by numerous vascular spaces and contains scattered large osteoclast type giant cells within the stroma and a loose fibrovascular stroma (hematoxylin-eosin, x100). C: Immunohistochemical reactivity for factor VIII was detected in vascular space (immunostaining, original magnification x100). D: Immunohistochemical reactivity for p53 was detected in osteoblastic cells, (immunostaining, original magnification x100). E: Immunohistochemical reactivity for MIB-1 was detected in scattered osteoblastic cells, (immunostaining, original magnification x100). F: Immunohistochemical reactivity for apoptosis was detected in some osteoblastic cells, (immunostaining, original magnification x100).*

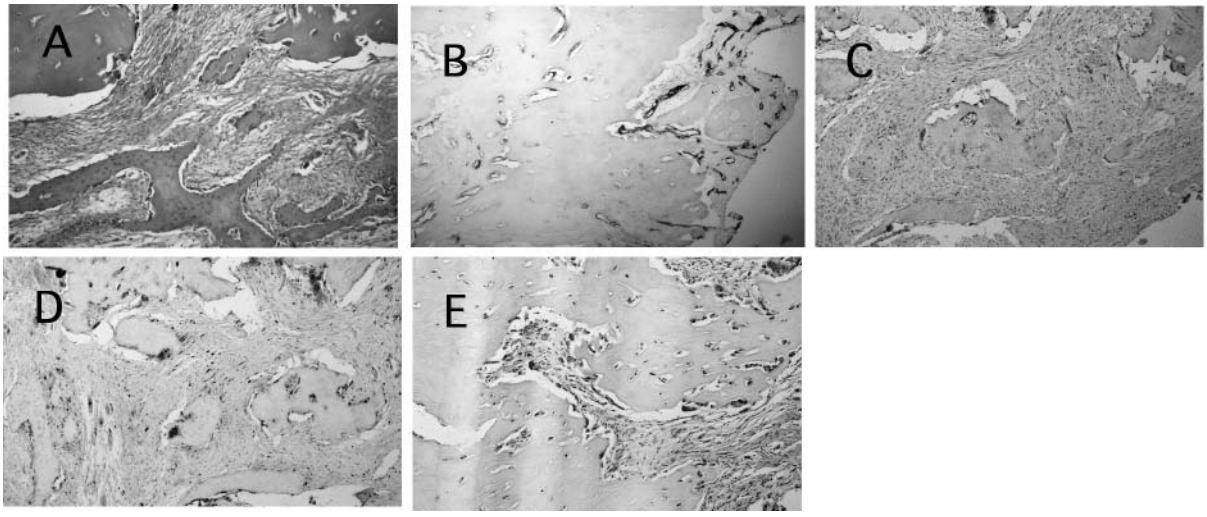

Figure 2. *Case 2. A: High-power microscopic view of a thin layer of irregular osteoid, bone and cement within a fibrovascular stroma consisting of hypercellular fibrous connective tissue (hematoxylin-eosin, x200). B: Immunohistochemical reactivity factor VIII was detected in vascular space. C: Immunohistochemical reactivity for p53 was detected in osteoblastic cells, (immunostaining, original magnification x100). D: Immunohistochemical reactivity for MIB-1 was detected in osteoblastic cells, (immunostaining, original magnification x100). E: Immunohistochemical reactivity for apoptosis was detected in osteoblastic cells, (immunostaining, original magnification x100).*

it was clearly separated from the apical third of the tooth root. From the purely histological standpoint, cementobastoma is characterized by interlacing trabeculae of mineralized tissue, which resemble cellular cementum and have a more eosinophilic appearance compared to the basophilic trabeculae seen in osteoblastoma.

Histologically, osteoid osteoma is composed of nidus that measure less than 1.5 cm and are surrounded by reactive sclerotic bone. The nidus consists of a highly vascularized, richly-innervated fibrous stroma containing interconnected trabeculae of osteoid and woven bone lined with osteoblasts and osteoclasts. These microscopic

features are identical to those of the osteoblastoma, and classically the distinction depends on the size of lesion; lesions under 2 cm are osteoid osteomas, while osteoblastoma are larger and occur in the femur, tibia and falanges and very rarely in the jawbones (5, 21).

With regard to fibrous dysplasia, whether monostotic or polyostotic, if accompanied by skin lesions, such as abnormal pigmentation of the skin, is termed Jaffe Liechtenstein syndrome, and by other abnormalities such as endocrinopathies is known as the McCunie-Albright Syndrome. In our second case, there were aspects, for example the ground glass appearance at radiography and the location in the body of the mandible, that might have led us to diagnostic error. However, the histological aspects were typical and were characterized by irregularly shaped trabeculae of immature woven bone in a cellular matrix, loosely arranged fibrous stroma. The bone trabeculae were not connected to one another and were curvilinear in shape, leaving no room for doubt.

Histological differential diagnosis of conventional osteoblastoma from osteoblastoma-like osteosarcoma, aggressive osteoblastoma and low-grade osteosarcoma, can be extremely difficult and in some cases even impossible (6, 22-28). Osteoblastoma-like osteosarcoma is considered a rare variant of osteosarcoma, accounting for between 1.1% to 1.4% of all osteosarcomas (27, 28). Pathological findings included areas resembling osteoblastoma with sheets of cells without bone production, variable amounts of lace-like osteoid, rounded nuclei with or without prominent nucleoli and admixed spindle stroma. The above reports suggested that a histologically proven permeative pattern provides a diagnostic indication of osteosarcoma (27). In a recent review, Rocca *et al.* disputed the relationship between benign histology and aggressive behavior; in an analysis of 55 cases they found no association between histological features and disease outcome (10). According to these authors, osteoblastoma is a benign neoplasm with various histological aspects all related to the activity of the osteoblastic neoplastic cell clone and the aggressive behavior is not related to particular histological features, but mainly to the localization of the neoplasm. They also observed that tumors involving short and flat bones were more aggressive than those occurring in the long bones. Finally, neither borderline lesions and transitional histological features were between osteoblastomas or low-grade osteosarcomas. Rather, the mitoses in neoplastic osteoblasts and the dysplastic changes in stromal and osteoblast-like cells were identified as the elements that enable the differentiation of osteoblastoma from low-grade osteosarcoma.

Osteosarcomas of the jaw usually develop in patients with a mean age of 33 years and the tumor cells may vary histologically from uniform round or spindle-shaped cells to highly pleomorphic cells. Anaplasia, atypical mitoses and a high rate of mitotic activity are frequently observed as well as infiltrative margins with lace-like or streamer osteoid. Cartilage production and sheets of malignant cells without osteoid production are also seen.

It is quite difficult to differentiate the aggressive form of osteoblastoma from the low-grade osteosarcoma. The aggressive form is an unusual tumor that occurs in an older patient population and is usually larger than the conventional osteoblastoma at diagnosis. It was reported that the aggressive form may have large sheets of osteoblasts twice the size of the osteoblasts seen in osteoblastoma (28). Both aggressive and low-grade osteosarcoma, develop more frequently in the vertebral column, tibia, femur and skull. Histological features of aggressive osteoblastoma include the presence of epithelioid osteoblasts and trabecular sheet-like osteoid, occasionally of chondroid matrix, as well as low mitotic activity and the absence of atypical mitoses (15). In many cases, the aggressive form has more multinucleated giant cells of the osteoclast type and more abundant atypical osteoid (13).

There is still no precise definition of aggressive osteoblastoma and many authors believe that the aggressive osteoblastoma may represent a low-grade osteosarcoma (19, 29-32).

The debate is still ongoing and at the moment the histological difference between the various forms lies in the cytological aspects of the neoplasm, for example the cytological atypia, hyperchromasia, pleomorphism, osteoid and mature bone, marked vascularity, epithelioid or cuboidal features of osteoblasts and the presence of giant cells (33, 34).

In our cases, there were no marked atypia or epithelioid osteoblasts and we did not find a permeative pattern in the periphery of the surgical specimens which might have pointed to either an osteoblastoma-like osteosarcoma, an aggressive osteoblastoma or a low-grade osteosarcoma.

Therefore, in order to identify other morphological parameters able to predict the behavior of these lesions, immunohistochemical analysis was performed for the following markers: factor VIII, useful for revealing the marked vascularity of these tumors; MIB-1, a monoclonal antibody that identified the ki67 antigen and is useful in determining the proliferation index; the apoptotic index and the tumor suppressor gene p53, which is implicated in regulation of the cell cycle. The MIB-1 index in a small series of classic osteoblastomas was ranged between 1.8 ± 0.8 and 3.7 ± 1.7% of cells (35, 36). Recently Bonar *et al.* reported a case with an MIB-Index of 15% (26). In our second case, MIB-1 was intensely positive, with a value well above this range. On the other hand, the positivity in some osteoblastic cells found in our first case was compatible with results reported by others (38). It is known that a higher rate of MIB-1 supports a diagnosis of osteoblastoma-like

osteosarcoma, but there were no aggressive features in our case (38). There was an apparent correlation between MIB-1 and apoptosis immunoreactivity. We found that increased MIB-1 reactivity was associated with high apoptosis and p53 positivity and that decreased MIB-1 was associated with high apoptosis. These features suggest that, in osteoblastic tissues, MIB-1, apoptosis and p53 expression are probably involved in the onset or development of the osteoblastoma.

The true recurrence rate of the aggressive variants is difficult to estimate. It has been reported that the recurrence rate of aggressive osteoblastoma is 50% and that of osteoblastoma is 13.6%, but to date distant spread has never been observed (13). Treatments reported range from local conservative curettage to a surgical approach for the complete removal of the tumor. Treatment depends on tumor size and site, although in some cases access was potentially severely mutilating (39). Recurrence is attributed to inadequate or conservative initial treatment, including incomplete local curettage or partial resection of the tumor and not to inherent behavior (34, 40). However, even with a limited conservative approach, complete resolution or regression have occurred and in some cases spontaneous regression took place after biopsy (41, 42). It has been claimed for cases at the maxilla that the tendency of this subgroup of osteoblastomas to recur is largely due to the inadequacy of the initial treatment (15-18). Moreover, apparently no special histological features exist that provide clues to the biological behavior of this neoplasm. Based on these various reports and findings, it is clear that the neoplasm has no constant behavior, and varies from case to case. Due to its significant tendency to recur and inconstant behavior, it should be treated surgically with a radical approach.

In conclusion, benign osteoblastomas are tumors with a significant recurrence rate, an inconstant behavior and do not metastatize. Early and accurate diagnosis followed by surgical treatment is of utmost importance for improving prognosis. The true nature of this tumor is not fully understood and its biological potential remains unclear (2, 29, 37, 43). The subdivision into benign and "aggressive" subgroups, the concepts of initial malignancy, and spontaneous malignant transformation, as well as the existence of low-grade osteoblastomas, all require further investigation. The neoplasm must be differentiated from benign tumors such as cementoblastoma, fibro-osseous dysplasia, osteoid osteoma and from malignant tumors, particularly low-grade osteosarcoma. Therefore, careful correlation of histopathological features and the immunohistochemical profile with clinical presentation and radiographic appearance may be necessary to achieve accurate diagnosis.

From the immunohistochemical standpoint, MIB-1, factors VIII, apoptosis and p53 are clearly expressed in the osteoblasts of patients with osteoblastoma. These findings suggest that the low MIB-1 reaction is accompanied by significant apoptosis and that reduced proliferation is accompanied by a high apoptosis rate and low p53 reactivity.

These results reveal that, in osteoblastic tissues, MIB-1, apoptosis and p53 expression are probably involved at the onset or development of the osteoblastoma, but the individual or combined roles of these markers are not yet clear. Further studies will be needed to determine the role of MIB-1, p53 and apoptosis in osteoblastomas.

Acknowledgements

We would like to thank B. Vergani (National Cancer Institute) for her assistance with the immunohistochemistry. This work was founded by grants from International Society for the Study of Comparative Oncology, Inc. (ISSCO, President HE Kaiser) Silver Spring, MD, USA and FUTURA-Onlus to A. Baldi.

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Received April 10, 2006
Revised July 4, 2006
Accepted July 7, 2006