Clinicopathologic study of 6 cases of epithelioid osteoblastoma of the jaws with immunoexpression analysis of FOS and FOSB

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Objective. The aim of this study was to describe the clinicopathologic features of a series of gnathic epithelioid osteoblastomas. As high levels of Proto-oncogene c-Fos proteins resulting from *FOS-FOSB* translocation were recently demonstrated in osteoblastomas, we also evaluated the immunoexpression of these proteins.

Study Design. Records of all cases of epithelioid osteoblastoma of the jaws were retrieved from oral pathology services, and their clinicopathologic and immunohistochemical data were collected. Immunohistochemistry was also performed by using anti-FOS and anti-FOSB antibodies.

Results. Six cases of epithelioid osteoblastomas were obtained, 4 in men and 2 in women, and they were mainly located in the posterior body of the mandible (n = 4). Radiographically, the tumors showed mixed radiolucent and radiopaque images, most with poorly defined margins. Microscopically, large epithelioid cells with eccentrically located nuclei predominated among osteoid and immature bone trabeculae. Sharp delineation from adjacent normal bone was observed in all cases. FOS immunostaining was diffuse and strong in the cytoplasm and nucleus of neoplastic cells in all cases, whereas FOSB was only focally positive, with few epithelioid osteoblasts showing nuclear staining.

Conclusions. Although epithelioid osteoblastomas of the jaws are locally aggressive, widespread metastasis does not occur, and, as with conventional osteoblastomas, there is wide expression of the FOS protein. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:191−199)

Osteoblastoma is a benign bone-forming neoplasm, accounting for approximately 1% of all bone tumors. It commonly affects the vertebrae and long bones, and only 11% of reported cases develop in the jaws, mostly in the posterior region of the mandible.[1] It is a slow-growing tumor, usually associated with pain, tenderness, or discomfort.[2]

Osteoblastomas show radiographic features consistent with a benign neoplasm, with well-defined margins and an expansile growth pattern; cortical perforation may be observed, illustrating the locally aggressive behavior of the tumor.[3] The microscopic features of osteoblastoma include woven bone haphazardly arranged and rimmed by large osteoblasts and may resemble osteosarcomas, making its diagnosis a potential histological dilemma.[4]

Eventually, osteoblastomas may be composed of sheets of prominent round osteoblasts with eosinophilic cytoplasm and eccentrically located nuclei with vesicular chromatin, revealing an epithelioid morphology.[3,5] These tumors, which have been termed *epithelioid osteoblastomas*, have been associated with a more aggressive clinical behavior and are, therefore, often referred to as *aggressive osteoblastomas*.[5,6]

A 3-way translocation involving chromosomes 1, 2, and 14 was identified in 1 osteoblastoma arising in the femur.[7] Cytogenetic and single nucleotide polymorphism array analyses showed copy number losses involving chromosome band 22 q12 in 2 aggressive osteoblastomas and in 1 case of the conventional subtype.[8] Recently, recurrent rearrangements of *FOS* and its paralogue, *FOSB*, have been described in skeletal osteoblastomas and osteoid osteomas.[9] Consistent with these findings, strong nuclear immunoreactivity of the

Statement of Clinical Significance

Epithelioid osteoblastoma of the jaws is a very rare variant that usually demonstrates a locally aggressive behavior but no widespread metastasis and shows expression of FOS protein. This lesion needs to be better recognized because of its resemblance to osteosarcoma.

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Proto-oncogene c-Fos protein in osteoblastoma cells was also reported.[9] However, the molecular alterations in osteoblastomas have not being previously investigated in tumors located in the jaws, particularly in the epithelioid variant of osteoblastomas. Therefore, in the present study, we aimed to identify the clinicopathologic features of 6 new cases of epithelioid osteoblastomas affecting the jaws and to assess the immunoexpression pattern of the FOS and FOSB proteins.

MATERIALS AND METHODS

Case selection, diagnosis, and clinicopathologic characteristics

Reports of all cases diagnosed as epithelioid osteoblastomas of the jaws were retrieved from the pathology files of the School of Dentistry of the Federal University of Rio de Janeiro (Rio de Janeiro/Brazil), Centro Clínico de Cabeza y Cuello (Guatemala City, Guatemala) and the School of Dentistry of the University of Pretoria (Pretoria, South Africa). Formalin-fixed, paraffin-embedded specimens were obtained, and 4-μm new histologic sections were stained with hematoxylin-eosin for confirmation of histopathologic diagnosis. Clinical and radiographic data were retrieved from patients' clinical charts. The data of the cases were reviewed by at least 3 authors (T.S.F.P., R.S.G., and F. P.F.) for confirmation of the diagnoses.

Clinicopathologic diagnosis was based on the following criteria: (1) epithelioid osteoblasts as the predominant cellular element (> 75%)[1]; (2) sharp host−tumor interface or mature bone in the periphery[10]; (3) absence of destructive tumor permeation or entrapment of host bone[4]; and (4) variable amounts of bone formation ranging from osteoid or immature woven bone to lamellar trabeculae. Epithelioid osteoblasts display eccentrically placed large vesicular nuclei with prominent nucleoli and abundant eosinophilic cytoplasm.

Immunohistochemistry

Immunohistochemical staining was performed by using standards protocols. Trilogy (Cell Marque, Rocklin, CA) was used for deparaffinization, rehydration, and unmasking. Blocking of endogenous peroxidase was performed with hydrogen peroxide/methanol. Sections were incubated with primary anti-FOS antibody, at 1:5000 dilution (produced in rabbit, F7799; Sigma-Aldrich, St. Louis, MO), or anti-FOSB antibody, at 1:50 dilution (clone 5 G4; CST, Danvers, MA), overnight at room temperature. The primary antibody was omitted in negative controls, and sections of normal bone were used as positive control. Dako EnVision + Dual Link System-HRP and Dako DAB + substrate chromogen system (Agilent, Santa Clara, CA) were used for detection. Slides were subsequently counterstained with Meyer's hematoxylin, and the results were descriptively reported. Other immunohistochemical reactions were performed for diagnostic purposes by using a variable panel of antibodies, depending on the diagnosis workflow of each case and each pathology service. These included pan-cytokeratin AE1/AE3, 34 βE12, CK8, carcinoembryonic antigen (CEA), smooth muscle actin, S100 protein, CD138, vimentin, neuron specific enolase (NSE), epithelial membrane antigen (EMA), and Ki67.

RESULTS

Case selection, diagnosis, and clinicopathologic features

Detailed clinical and radiographic features of all 6 epithelioid osteoblastomas are summarized in Table 1. Four male patients and two female patients were included, and the mean age at diagnosis was 29.8 years (range 9−69 years). The mandible was affected in 4 cases and the maxilla in 2 cases.

Radiographic images of the tumors showed variable mixed radiolucency and radiopacity, with poorly defined (n = 4) or well-defined (n = 2) margins, resulting in expansion of the vestibulolingual cortical bones. Neither cortical perforation nor periodontal space widening was observed (Figure 1).

Grossly, surgical specimens presented a heterogeneous cut surface ranging in color from a whitish hue to tan-brown to black (Figure 2). Microscopically, in all cases, the edges of the tumors were compressed against adjacent normal bone, rather than showing permeation or entrapment. The adjacent bone limits were sharply demarcated in some areas (Figure 3A), whereas in other areas, tumor expansion pushed the borders. Tumors were characterized by predominance of large epithelioid cells with eccentrically placed nuclei and abundant eosinophilic cytoplasm (Figure 3B). Prominent nucleoli and mild cellular pleomorphism were other features of neoplastic cells (Figure 3C). These epithelioid osteoblasts were cohesively arranged in sheets of cells or loosely dispersed in the stroma (see Figures 3B and 3C). Mitotic figures were scarce, and no atypical mitotic figures or areas of tissue necrosis were observed. Case 5 showed focal areas of vascular invasion. Large epithelioid osteoblasts with displaced nuclei were scattered inside a blood vessel (Figure 3D).

In 2 cases, the bone matrix was concentric, resembling the so-called Liesegang rings, as found in calcifying epithelial odontogenic tumors. Large polyhedral cells with pale cytoplasm interspersed these calcifications, forming sheets and islands. Well-defined cell borders were visible in some areas, favoring an epithelioid phenotype (Figures 4A and 4B). Bone matrix was present in different stages of maturation, with osteoid

Table 1. Clinicopathologic information of epithelioid osteoblastoma cases

#	*Age (years)*	*Gender*	*Localization*	*Clinical features*	*Radiographic description*	*Follow-up*
1	69	F	Right posterior mandible	Painful swelling	Ill-defined mixed radiolucent−radiopaque image	No recurrence in 2 years of follow-up
2	31	M	Left posterior mandible	Painful swelling	Ill-defined mixed radiolucent−radiopaque image with vestibular cortical expansion, thinning, and destruction	NA
3	33	F	Left posterior maxilla	Pain and displacement of superior premolars	Well-defined mixed radiolucent−radiopaque image with a radiolucent rim	NA
4	21	M	Right posterior mandible	Swelling	Ill-defined mixed radiolucent−radiopaque image	No recurrence
5	9	M	Left posterior maxilla and maxillary sinus	Swelling	Ill-defined mixed radiolucent−radiopaque image with vestibular cortical expansion, thinning, and destruction	No recurrence in 1 year of follow-up
6	16	M	Right posterior mandible	Swelling and displacement of inferior premolars	Well-defined mixed radiolucent−radiopaque image	No recurrence

F, female; *M,* male; *NA,* not available.

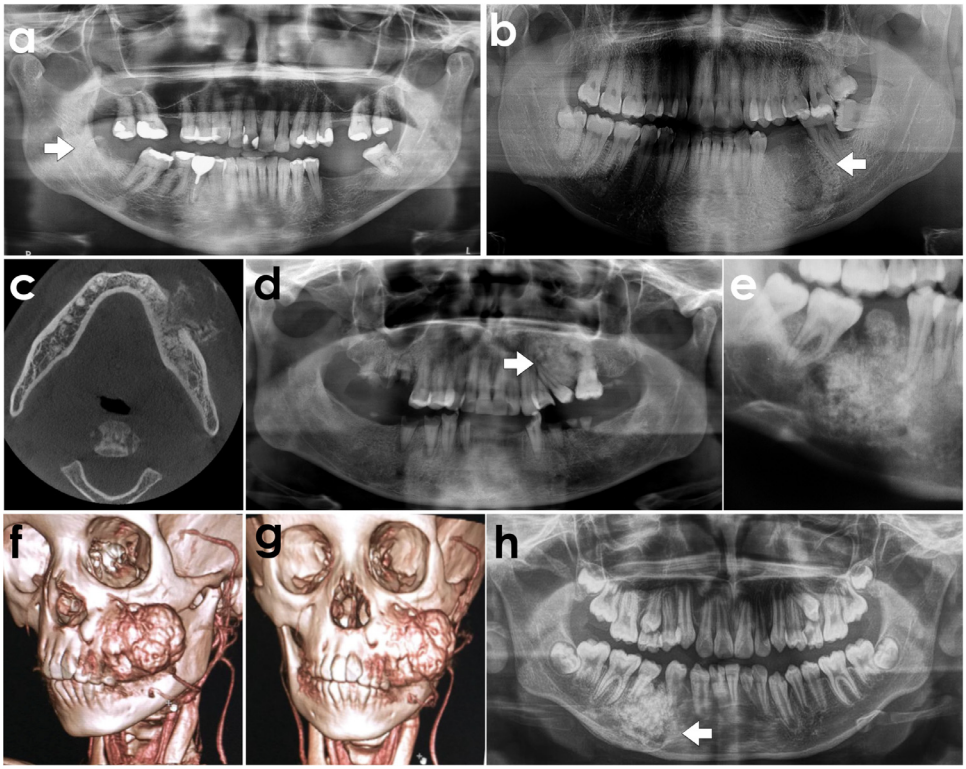

Fig. 1. Radiographic and computed tomography (CT) images of epithelioid osteoblastomas. Epithelioid osteoblastomas produced a mixed radiolucent−radiopaque image with ill-defined borders in cases 1 **(A)** and 2 **(B, C)**. Case 3 **(D)** showed tooth root displacement and well-defined limits. Case 4 **(E)** exhibited a mixed and ill-defined image in the previously extracted first molar site. A 3-dimensional reconstruction from the CT scan of case 5 **(F, G)** showed a large expansive lesion in the alveolar maxillary process. The mixed image in case 6 **(H)** showed the lesion surrounded by a sclerotic margin.

randomly arranged within stromal areas and surrounded by epithelioid osteoblasts (Figures 4C and 4D). Congo-red staining was positive in 1 case, and the extracellular matrix showed green-yellow birefringence under polarized light microscopy (Figures 4E and 4F).

Immunohistochemical reactions were performed to confirm the diagnosis of osteoblastoma and to differentiate it mainly from low-grade osteosarcomas and calcifying epithelial odontogenic tumors. The tumor cells were negative for cytokeratin AE1/AE3, 34 βE12, CK8, CEA, SMA, S100 protein, and CD138, whereas positivity was observed for vimentin, NSE, and EMA. The proliferative index, estimated by performing Ki-67, was below 5% (Figure 5).

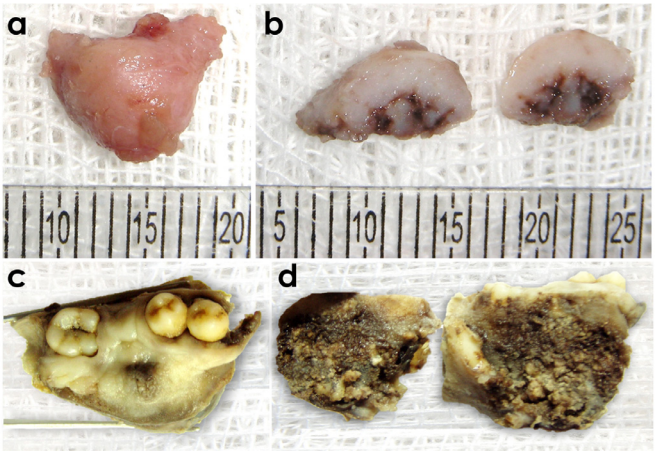

Fig. 2. Gross image of epithelioid osteoblastomas. In gross appearance, tumor of case 1 was roundish **(A)** and cut surface was grayish, with dark central areas **(B)**. Case 4 showed areas of apparent superficial necrosis and involvement of inferior right premolars and second molar **(C)**. Cut surfaces were coarsely rough and brownish with cream colored spots **(D)**.

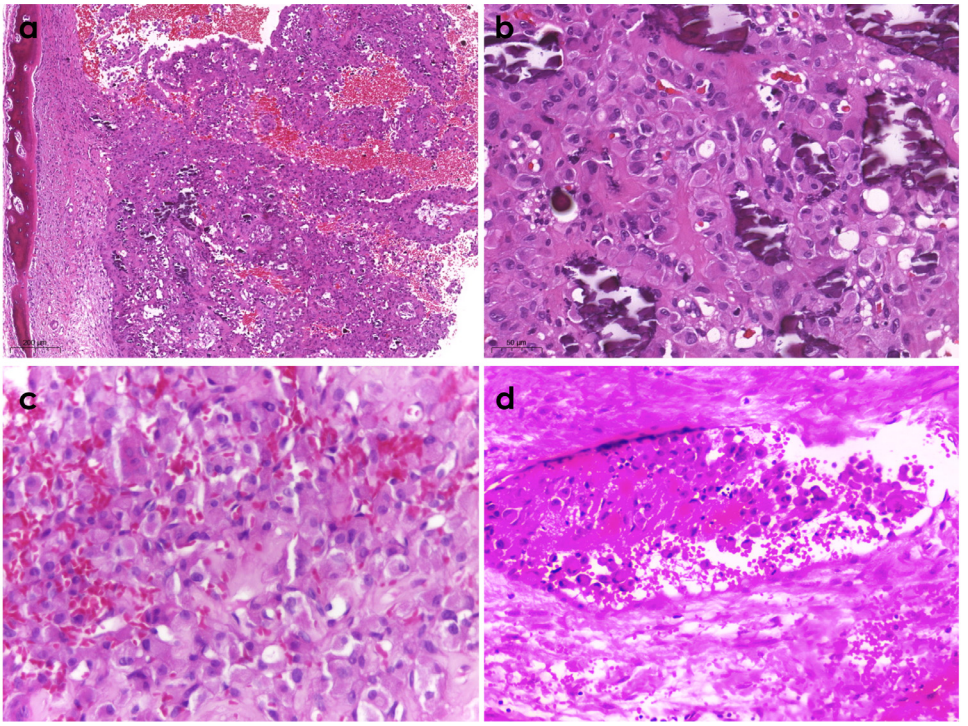

Fig. 3. Histopathologic features of epithelioid osteoblastoma. The tumor shows no permeation into adjacent bone (**A,** case 2) (hematoxylin-eosin [H&E] staining; original magnification × 50). Epithelioid osteoblasts may form sheets interspersed between bony trabeculae (**B**, case 2) (H&E; original magnification × 200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05737.* Individually, neoplastic osteoblasts are large, with eccentrically placed nucleus, prominent nucleoli, and abundant eosinophilic cytoplasm (**C,** case 1) (H&E; original magnification × 200). Large epithelioid osteoblasts invading vascular spaces (**D,** case 5) (H&E; original magnification × 200) were seen in 1 case.

All patients were surgically treated, but the approach varied from surgical resection to tumor enucleation. In all cases with available follow-up information, patients remain free of disease with no evidence of tumor recurrences.

FOS and FOSB protein immunohistochemistry

A strong nuclear immunoreactivity of the FOS protein was recently reported in conventional osteoblastomas.[9] Therefore, we investigated the immunoexpression of the FOS and FOSB proteins in this set of

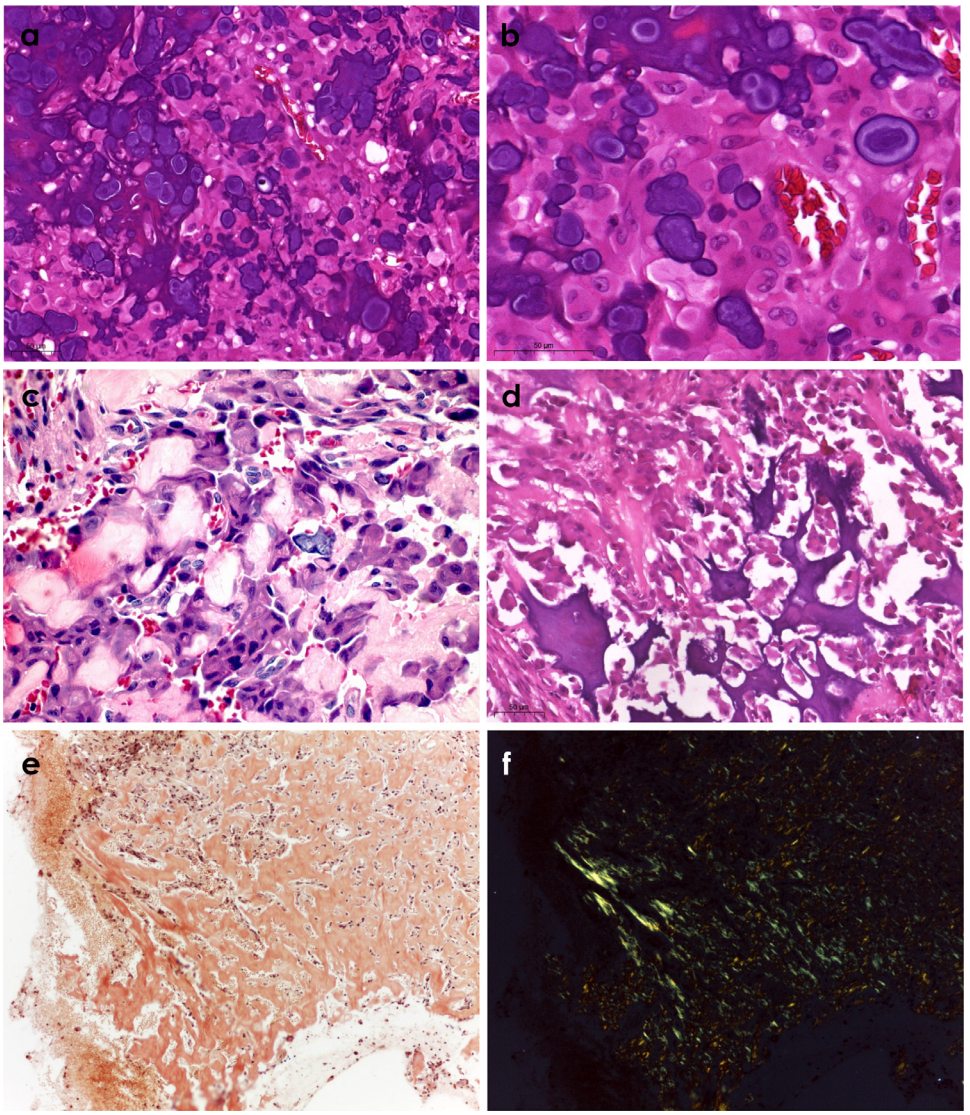

Fig. 4. Microscopic aspect of mineralized component of epithelioid osteoblastoma. Formation of concentric calcifications (Liesegang rings) resembling microscopic features of calcifying epithelial odontogenic tumor (**A, B,** original magnification × 200 and × 400, respectively). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05741.* Plump osteoblasts are visualized rimming bone matrix (**C,** case 4) and osteoid (**D,** case 5) (hematoxylin-eosin [H&E] staining; original magnification × 20). One case showed Congo-red staining (**E,** case 1) and green-yellow birefringence under polarized light (**F,** case 1) (original magnification × 50).

epithelioid osteoblastoma cases. We observed that FOS immunoreactivity was diffuse and strong in all cases, with epithelioid osteoblasts arranged in sheets and entrapped within the bone matrix showing nuclear and cytoplasmic positivity (see Figure 5E). The osteocytes and osteoblasts rimming the trabeculae also exhibited FOS immunoreactivity in both neoplastic and peripheral reactive bones. FOSB immunostaining, however, was only focally found in all 6 evaluated cases, with a few scattered epithelioid osteoblasts showing nuclear positivity. FOSB positivity was also observed in the osteocytes and osteoblasts surrounding healthy bone trabeculae (see Figure 5F).

DISCUSSION

Epithelioid osteoblastoma is a rare benign neoplasm with clinical, radiographic, and microscopic features that are similar to low-grade osteosarcoma. Therefore, its accurate diagnosis may be challenging even for expert pathologists, even more so when only small biopsy samples are available for analysis. Moreover, a very rare microscopic variant of osteoblastoma rich in epithelioid neoplastic cells requires a more complex diagnostic workflow. Therefore, in this report, we have attempted to better characterize the clinicopathologic features of this rare entity by describing a series of 6 new cases of epithelioid osteoblastomas affecting the

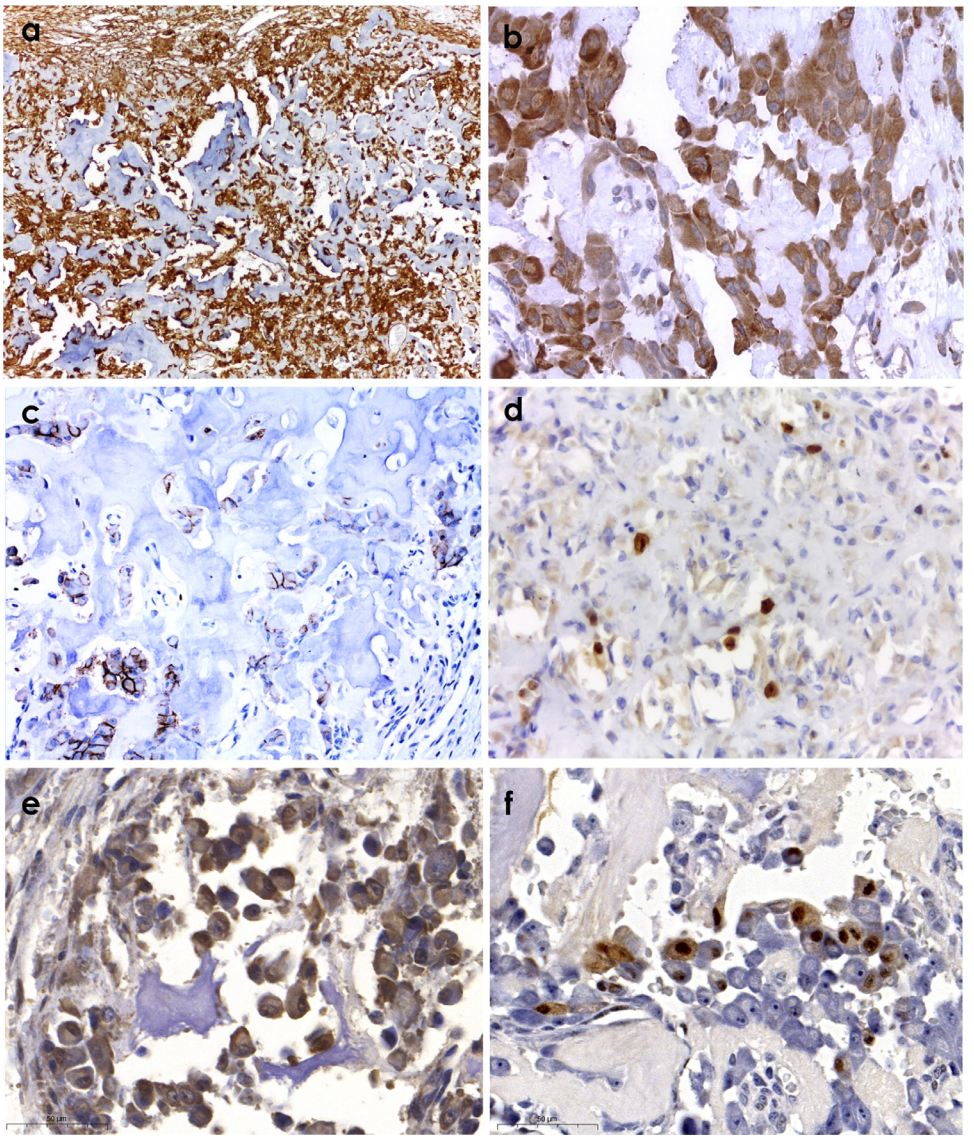

Fig. 5. Immunostaining profile of epithelioid osteoblastoma. Vimentin (**A,** case 1), neuronal specific enolase (**B,** case 4), and epithelial membrane antigen (EMA) (**C,** case 4) were positive. Low Ki-67 proliferative index (**D,** case 1) (original magnification × 200 and × 400). Epithelioid osteoblasts show intense nuclear and cytoplasmic FOS positivity (**E,** case 5) (original magnification × 400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05739.* FOSB was focally positive in epithelioid osteoblasts (**F,** case 5) (original magnification × 400).

gnathic bones. High levels of the FOS protein resulting from *FOS-FOSB* translocation were recently demonstrated in osteoblastomas,[9] and for this reason, we also evaluated the expression of these proteins in our series to better understand the pathogenesis of this tumor.

Epithelioid osteoblastomas develop in different parts of the skeleton, such as the skull,[11,12] clavicle,[13] and long bones.[14] Few cases have been reported in the jaws, with the mandible more frequently affected than the maxilla.[5,10,14-19] In our series, 4 tumors (67%) affected the mandible, and only 2 (33%) affected the maxilla. Upon review of the literature, we found some reports of epithelioid/aggressive osteoblastomas showing microscopic features similar to our cases.[10,15,18,20] The slow tumor growth was frequently associated with pain,[10,15,18-21] facial asymmetry, and tooth displacement.[10,19] On radiographic images, the lesions often have a mixed radiolucent/radiopaque appearance with well-defined borders, consistent with its benign nature.[5,10,15,19] Periosteal reaction and peripheral bone sclerosis[5] have also been reported. Well-defined margins were observed in only 2 cases in our series. Although an ill-defined lytic image was observed in a few cases reported in the literature,[18,20] in our series, we found 4 cases with poorly defined margins.

The histopathologic appearance of the tumors in our cases and in the previously reported cases encompassed osteoid and bone trabeculae surrounded by epithelioid osteoblasts. These neoplastic cells may be focally arranged in cords and solid sheets. Variable levels of mineralization and different stages of maturation of the calcified component were present, and peripheral maturation of "blue bone" to trabeculae of woven bone was a frequent finding.[18,19] Two of our cases showed a different concentric pattern of the mineralized component, resembling the so-called Liesegang rings. Osteoclast-like multinucleate giant cells, which have been frequently reported,[15,18,19] were observed occasionally in our cases.

Differential diagnosis includes benign lesions, such as osteoid osteoma, cementoblastoma, calcifying epithelial odontogenic tumor, and fibro-osseous lesions, as well as malignant tumors, particularly low-grade osteosarcoma.[22] Conventional osteoblastomas and cementoblastomas are microscopically similar, and the differentiation is classically based on the connection of cementoblastomas with a tooth with no intervening periodontal ligament.[23] Large cells may also be present in cementoblastomas, but these are not the predominant cell type and are only focally observed, thus differentiating these tumors from epithelioid osteoblastomas. In our series, no fusion with the roots of adjacent teeth was observed.

The clinical and radiographic features of epithelioid osteoblastoma may also resemble juvenile ossifying fibroma, a fibro-osseous lesion that affects mostly children and young adults.[24] Microscopically, the presence of sheets of epithelioid osteoblasts and the absence of a highly cellular fibrous stroma, typical of juvenile ossifying fibroma,[25] supported the diagnosis of epithelioid osteoblastoma in our cases.

Epithelioid osteoblastomas of the jaws may present histopathologic similarities to calcifying epithelial odontogenic tumors, which are composed of sheets of large polyhedral epithelial cells. However, the nonepithelial nature of these cells is confirmed with cytokeratin analysis, which shows negative results in cases of epithelioid osteoblastomas,[10] as demonstrated in our series. Although the cell boundaries of epithelioid osteoblasts may be evident in some cases, intercellular bridges are not seen, as in calcifying epithelial odontogenic tumor. The amorphous material in this odontogenic tumor stains with alpha-amyloid and Congo-red stains; the latter produces "green apple birefringence" under polarized light.[10] The extracellular matrix in one of our cases of epithelioid osteoblastomas also showed Congo-red staining and green-yellow birefringence. The positivity suggests that the tumor may produce amyloid, but we do not have a plausible explanation for this finding. Further studies are necessary to clarify the nature of these deposits.

The osteoblastic tumor cells show positivity for vimentin,[10,20] as we also observed in our cases. Salmen et al. demonstrated immunoreactivity to CD99 and INI-1.[20] In our series, immunoexpression of NSE and EMA were also detected in 1 case. Vigneswaran et al. assessed immunoreactivity for osteocalcin and demonstrated strong positivity in trabecular osteoid and neoplastic woven bones.[10] A low proliferative index, estimated by performing Ki-67, was noted in our series, in accordance with previously reported cases.[10] CD138 (syndecan-1) is a transmembrane heparan sulfate proteoglycan that is particularly expressed in epithelial cells and neoplasms, including squamous cell carcinomas.[26] Its expression is recognized in cells with plasmacytic differentiation in hematologic disorders.[27] However, because CD138 expression has also been described in benign and malignant bone-forming neoplasms,[28] we investigated its expression pattern in all 6 cases in this series, but all cases were negative.

Osteoblastomas also show histologic similarities to osteoid osteoma. This small benign bone-forming tumor is a nonprogressive lesion, with patients complaining of nocturnal pain in most of the cases.[29,30] Microscopically, both tumors demonstrate similar findings, and differentiation is based on size because lesions that are radiographically greater than 2 cm in size are designated as osteoblastomas.[29] In all 6 cases in our series, the tumors had radiographic dimensions greater than 2 cm. Swelling followed by progressive pain and cortical expansion are clinical findings of epithelioid osteoblastomas and were also observed in our cases.[5,19,21] However, locally aggressive behavior of lesions may be observed, and some may grow to large dimensions, causing significant bone destruction, but no metastasis. These lesions are referred to as *aggressive osteoblastomas*, a denomination commonly used as a synonym for *epithelioid osteoblastoma* by some authors.[1,13] However, not all aggressive osteoblastomas show the epithelioid phenotype, and not all epithelioid osteoblastomas demonstrate aggressive behavior, which is more likely to be associated with other parameters, such as the site affected and the therapeutic approach used to treat patients.[1,10,14,20,22] Supporting this notion, a large clinicopathologic study of osteoblastomas showed that this histopathologic characteristic is not an accurate indicator of clinical behavior because most of these tumors do not progress to an aggressive clinical course.[1] Therefore, we favor the term *epithelioid osteoblastoma* because the lesion may or may not be clinically aggressive.

Epithelioid osteoblastomas may show some level of cytologic atypia, although the mitotic index remains low. However, osteosarcomas usually demonstrate greater pleomorphism and atypical mitosis, which are associated with a higher, although variable, mitotic

index.[3] The immunoreactivity of CDK4 and MDM2 was recently described as a helpful auxiliary tool for the diagnosis of low-grade osteosarcoma, which usually does not demonstrate evident cytologic pleomorphism and presents a lower proliferative index.[31] However, the expression of these markers in epithelioid osteoblastomas is uncertain and remains to be investigated. As an attempt to exclude the diagnosis of osteosarcoma, analysis of the surgical margins of the tumor is highly contributory. Maturation of the edges with peripheral bony trabeculae that are well separated from surrounding normal bone is observed in osteoblastomas,[18,19] with no foci of infiltration or permeation into the adjacent structures, as observed in osteosarcomas.[4] However, it is important to highlight that another microscopic variant of osteoblastoma may present multiple foci of neoplastic cells giving rise to a multifocal growth pattern that may simulate tumor permeation. This phenomenon is usually associated with the presence of epithelioid osteoblasts, and it is classified as epithelioid multinodular osteoblastoma.[14,17,32] In our sample, all 6 cases contained large epithelioid osteoblasts diffusely arranged in sheets and surrounding woven osteoid and trabeculae with no cluster formation, absence of multinodular pattern, and lack of infiltrative features. Vascular invasion by epithelioid osteoblasts was an intriguing finding in one of our cases. However, it was not interpreted as a sign of malignancy because no other microscopic feature indicated the diagnosis of a malignant condition. Intravascular cluster of neoplastic cells has been previously reported in benign tumors, such as pleomorphic adenoma, but no correlation with prognosis and potential for metastasis has been established.[33,34]

Rearrangements of *FOS* and *FOSB* were recently identified by Fittall et al. in osteoblastomas and osteoid osteomas through whole genome sequencing (WGS).[9] These rearrangements were not observed in their main differential diagnoses, particularly osteosarcomas, indicating that this molecular event would be a marker to confirm the diagnosis of osteoblastomas/osteoid osteomas.[9] Fittall et al. also reported strong FOS immunoreactivity in osteoblastomas, whereas only 1 osteosarcoma showed comparable intensity and distribution pattern.[9] In our series, all 6 cases presented FOS and FOSB immunoexpressions, with a strong nuclear and cytoplasmic staining for FOS, and only focal nuclear immunopositivity for FOSB, consistent with previous reports.[9] Additional studies are necessary to further understand the significance of the expression of these proteins in the differential diagnosis of bone tumors.

CONCLUSIONS

The present study identified the clinicopathologic features of a very rare epithelioid variant of osteoblastoma of the jaws that usually demonstrates locally aggressive clinical behavior but has no metastatic potential. We also demonstrated that the FOS and FOSB proteins, previously assessed in conventional osteoblastoma,[9] are also expressed in the epithelioid variant of this neoplasm.

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