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## FOS Rearrangement and Expression in Cementoblastoma

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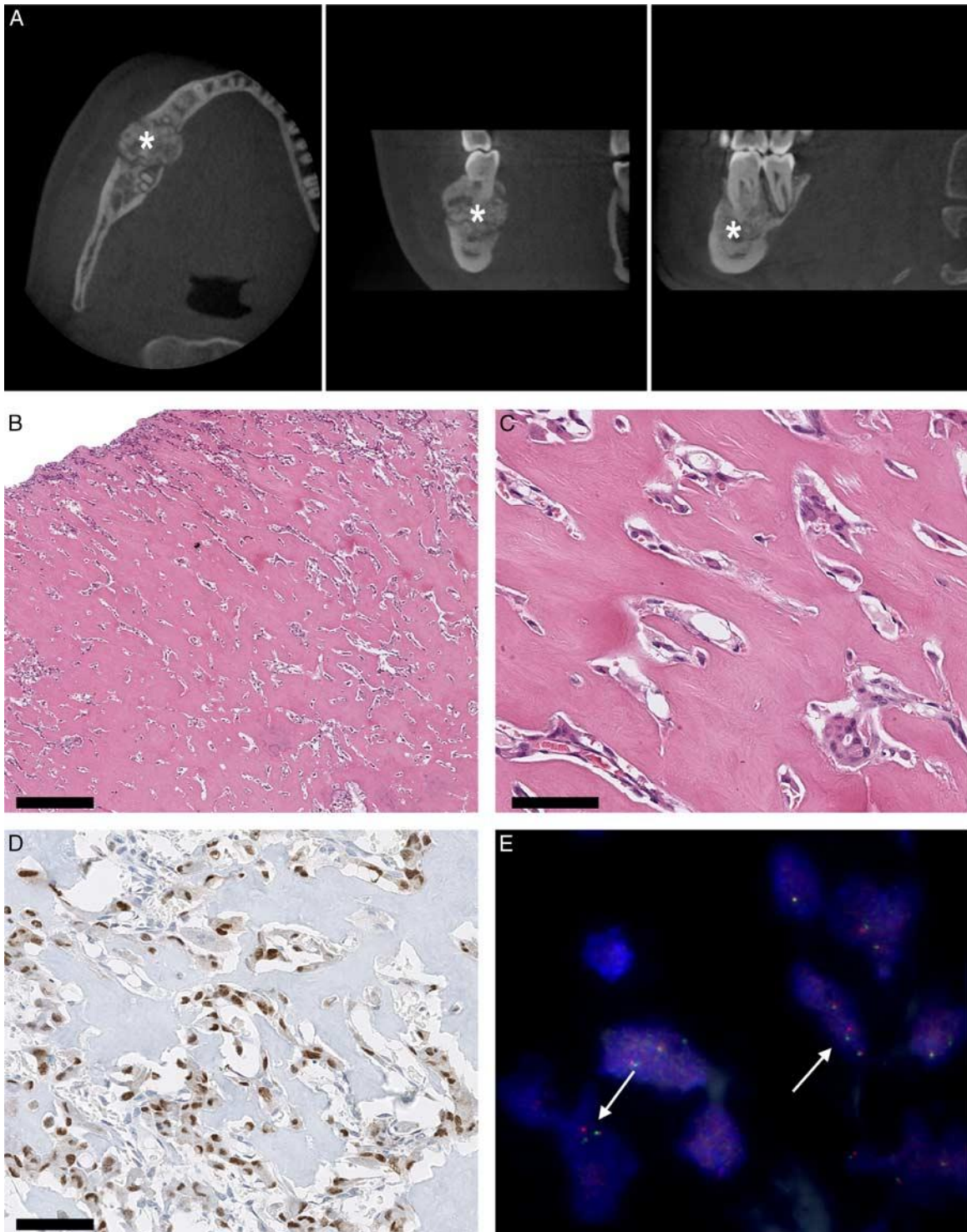
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**FIGURE 1.** Radiology, morphologic findings, c-FOS expression, and FOS rearrangement in cementoblastoma. A, Computed tomography images show a well-defined lesion (~2 cm) in the mandible on the right side (asterisks). The mass demonstrates an ossifying matrix and is closely related to the root of element 4.6 which shows erosion. There is a cortical interruption on both the buccal as well as the lingual side of the mandible. B, Immature and strongly mineralized matrix formation attached to the root of a tooth. C, Activated cementoblasts and a well-vascularized fibrotic stroma surrounding the lesional bone matrix. D, Strong c-FOS nuclear and cytoplasmic expression in lesional cementoblasts intermingled with negative normal cells. E, FISH using split-apart probes for *FOS* shows a segregated red and green signal in cementoblastoma, indicating a *FOS* rearrangement (arrows).

**TABLE 1.** Overview of Clinical Characteristics and Results of c-FOS Immunohistochemistry and FISH in Our Series of Cementoblastoma

Case	Sex	Age (y)	Tumor Size (mm)	c-FOS IHC	FOS FISH
Basel 1	Female	32	19	Negative	Failed
Basel 2	Female	25	23	Negative	Failed
Basel 3	Female	24	17	NA	Failed
Basel 4	Female	47	17	NA	Failed
Basel 5	Female	12	15	Negative	Failed
Basel 6	Male	22	28	Negative	Failed
Basel 7	Female	16	17	Positive	Positive
Basel 8	Male	13	21	Positive	Failed
Basel 9	Female	13	32	Positive	Failed
Basel 10	Female	14	10	Positive	Positive
Basel 11	Male	22	35	Positive	Failed
Basel 12	Female	12	34	Positive	Failed
LUMC 1	Male	16	25	Positive	Failed
LUMC 2	Female	20	30	Positive	Failed
LUMC 3	Female	13	15	Positive	Failed
LUMC 4	Male	19	16	Positive	Positive

IHC indicates immunohistochemistry; NA, not applicable.

between were occupied by a monomorphic and densely vascularized fibroblastic stroma lacking cytologic atypia. All tumors were sharply delineated and demonstrated the obliteration of the periodontal ligament space by lesional matrix.

We observed strong and diffuse staining of c-FOS in 71% of cases (10/14, Table 1, Fig. 1D), which is in concordance with the expression observed in osteoblastomas ranging from 57% to 83%.<sup>5</sup> All positive cases in our series showed a strong nuclear expression of c-FOS in >50% of tumor cells. Of note, the tumor cells were intermingled with normal cells such as stromal cells and osteoclast-like giant cells.

In 3 cases of cementoblastoma with strong c-FOS expression, we were able to identify a *FOS* rearrangement by FISH (Table 1, Fig. 1E). This is in line with the observed correlation of c-FOS overexpression and *FOS* rearrangements in osteoblastomas.<sup>4,5</sup> Notably, due to varying amounts of intermingled non-neoplastic cells, the percentage of split signals varied between cases, and was in some areas as low as 5% (LUMC case 4). In the residual cases (n = 13) no hybridization signals could be detected, most likely due to aggressive acid decalcification of the tumor samples. In the study by Lam and colleagues, it was furthermore shown that long decalcification times particularly affect c-FOS immunostaining that can result in false-negative results. This mechanism might explain the lack of staining for c-FOS in 4 cases of our study.

## DISCUSSION

Since cementoblastomas show a close relationship between the roots of the related teeth, it is believed to originate from cells of the inner dental follicle destined to become cementoblasts,<sup>6</sup> while osteoblastomas and osteoid osteomas are supposed to be derived from osteoprogenitor cells present in the entire skeleton.<sup>1</sup> However, this supposed difference in histogenesis is not translated into a different morphology, as cementoblastoma, osteoblastoma, and osteoid osteoma are histologically nearly identical.<sup>7</sup>

It has been hypothesized before that cementoblastomas might primarily develop as “conventional” osteoblastomas in the tooth-bearing areas of the jaws and secondarily become connected to a tooth.<sup>8</sup> Osteoblastomas and cementoblastomas both occur mostly in the second to third decades of life, recommended treatment is similar and comprises complete surgical excision, both entities may recur following incomplete removal. Here, we demonstrate that both lesions share the same molecular pathogenesis based on the presence of *FOS* rearrangements, adding further proof that cementoblastomas and osteoblastomas/osteoid osteomas indeed form a spectrum of the same disease.

*FOS* belongs to the *FOS* family of transcription factors that together with the *Jun* family members form a group of AP-1 proteins which bind to so-called TPA-responsive elements in the promoter and enhancer regions of target genes.<sup>9</sup> Therefore, *FOS* proteins regulate and influence various biological processes, including cell proliferation, differentiation, and survival. During normal osteoblast maturation, *FOS* and other members of the *FOS* family are highly expressed.<sup>10</sup> Similar to osteoblastoma, recurrent rearrangements of *FOS* or *FOSB* are also found in vascular tumors such as *FOS*-rearranged epithelioid hemangioma, and *FOSB* fusions are described in atypical epithelioid hemangioma and pseudomyogenic hemangioendothelioma.<sup>11–14</sup>

Histologically, many features of cementoblastoma can be encountered also in osteoblastoma, a radiologic correlation is, therefore, essential to demonstrate the connection with the root of a tooth in the case of cementoblastoma. The same holds true also for osteosarcoma which generally presents more aggressively on imaging analyses and shows cellular atypia typically lacking in cementoblastoma. The expression of c-FOS alone, however, can be observed also in a smaller subset of osteosarcomas (in 14%) and even in osteoblasts of reactive new bone formation.<sup>4,5</sup>

Since the percentage of actual tumor cells can be very low (exemplified by LUMC case 4) and FISH testing for *FOS* rearrangements often fails due to prior tissue decalcification, the correlation between morphology and radiology remains the cornerstone in the diagnosis of cementoblastomas and its differential diagnoses. In conclusion, our study shows that cementoblastomas not only share morphologic features but also harbor similar *FOS* rearrangements and c-FOS expression like osteoblastomas/osteoid osteomas, suggesting that cementoblastomas are part of the spectrum of the same disease localized at the root of teeth. Although the use of c-FOS immunohistochemistry is limited in its differential diagnosis, confirming the presence of a *FOS* translocation using FISH, whenever possible, can be of aid in diagnostic challenges.

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