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Differential Expression of Periostin in the Tumor Microenvironment of Jaw Bone Lesions: A Cross-Sectional Immunohistochemical Analysis

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KEYWORDS

POSTN, Bone tumor, Fibrous dysplasia, Osteosarcoma, Osteoma, Osteomyelitis, Paget's disease, Health risk

ABSTRACT:

Introduction: Periostin is an extracellular matrix protein important in bone development, remodelling, and modulation of the tumour microenvironment. It has been of interest because its dysregulation has been detected in jawbone lesions and has been suggested as a diagnostic and prognostic indicator.

Objectives: To quantitatively assess the expression levels of periostin in a spectrum of neoplastic and non-neoplastic lesions of the jaw and to clarify the role of periostin in disease pathogenesis.

Methods: 55 formalin-fixed, paraffin-embedded specimens were examined, comprising osteosarcoma (n = 10), fibrous dysplasia (n = 10), osteoma (n = 10), Paget disease (n = 10), osteomyelitis (n = 10), and normal bone controls (n = 5). A monoclonal anti-periostin antibody was used to perform immunohistochemical staining, and the level of expression was evaluated by a combined intensity and proportionality scoring system. The Kruskal-Wallis test and post hoc comparison were used to perform statistical analysis.

Results: Periostin expression was significantly elevated in fibrous dysplasia (2.7 ± 0.5) and osteoma (2.6 ± 0.5), followed by osteosarcoma (1.8 ± 0.6) and Paget's disease (1.1 ± 0.4), compared to normal bone (0.4 ± 0.2) and osteomyelitis (0.2 ± 0.1) ($p < 0.001$). High immunoreactivity of periostin was localized to the osteoid matrix and fibrous stroma, in areas of elevated vascularity and fibrosis. There was a considerable positive relationship between periostin expression and osteoid formation, stromal activity and angiogenesis ($p < 0.05$).

Conclusions: The results identify periostin as an important mediator of extracellular matrix remodelling and tumor-stroma interactions in jaw lesions. Its differential expression highlights its possible application as a diagnostic biomarker as well as a therapeutic target in bone pathology.

1. Introduction

The jawbone is an important part of the craniofacial complex which can be affected by various pathological conditions that not only affect oral health but also overall health. They may be caused by trauma, hormonal changes, low-grade chronic inflammation, and other disorders tumors and cysts. Of the tumors in the jaw, 45% were fibro-osseous lesions and 55% were ontogenic. Both the cysts and tumors were more prevalent in the mixed dentition stage. The tumors were not only prevalent in the mandibular anterior part of the jaw but showed a male preponderance. Approximately 1% of jaw tumors consist of malignant tumors, and the most prevalent of these are osteogenic sarcomas [1].

Jaw bone lesions are a special challenge because of their complex nature and different etiologies. Radiography, computed tomography (CT), and histopathological examination are traditional diagnostic modalities that cannot be neglected, but they have limitations in their capacity to identify lesion behavior and prognosis, which highlights the need to complement them with biomarkers [2,3]. Breaking down the molecular markers of a particular jaw bone lesion, clinicians can improve the quality of diagnosis and construct treatment plans that consider the profile of a particular patient [4].

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Periostin is a multifunctional matricellular protein that has become an important factor in bone biology, influencing multiple processes in bone development, remodelling, and repair. It communicates with Integrin receptors in cell surface, collagen and other matricellular proteins in the microenvironment to cause cell-cell adhesion and fibrillogenesis [5]. Its expression is also highly controlled during physiological bone turnover, and is imbalanced in various pathological diseases, such as cancer, osteoporosis, and inflammatory bone disease [6,7]. Although periostin plays a well-established role in bone homeostasis, the role of periostin in jawbone pathology is still poorly understood.

In addition, the interaction between periostin and other signalling pathways involved in bone homeostasis is dynamic, which highlights its potential as a therapeutic target [8]. New pharmacological modulators of periostin expression or activity show potential in reducing bone resorption, stimulating osteogenesis, and even suppressing tumour growth in jaw lesions. Consequently, a comprehensive understanding of periostin's intricate network of interactions within the bone microenvironment is imperative for the development of targeted therapeutics aimed at mitigating morbidity and improving patient outcomes.

2.Objective

The current study aims to assess the expression of periostin in common bone lesions of the jaw, elucidating their potential role in the pathogenesis of these lesions.

3. Methods

3.1.Sample selection

The institution's standard review board gave its approval prior to the start of the study (App no: SRB/SDMDS/17/OMP/02). The study material consisted of samples of neoplastic and non-neoplastic jawbone lesions namely Fibrous dysplasia (n=10), osteosarcoma (n=10), osteoma (n=10), osteomyelitis (n=10) and Paget's disease (n=10). Samples of normal bone (n=5) were taken from wide jaw resection specimens as the control for the study. The hard tissue specimens were decalcified in 10% formic acid, fixed in 10% buffered formalin and routinely processed. Formalin-fixed paraffin embedded blocks of the cases were used to obtain sections stained with hematoxylin and eosin for histological confirmation of the diagnosis in all cases.

3.2. Immunohistochemical procedure

Positively charged slides were used to pick up the 2-3µm slices from the formalin fixed paraffin embedded blocks of these individuals. The sections underwent xylene deparaffinization, alcohol dehydration, and distilled water rinsing. Heat-induced epitope retrieval of antigen was carried out with citrate buffer and the pressure cooker method (pH 6.0). Following that, there was a 5-minute protein block and a 5-minute endogenous peroxide block. The mouse monoclonal periostin primary antibody (Santacruz Biotechnology, United States) was incubated with the sections for one night at 4°C.

The Dako Envision Kit Detection System [DAKO Denmark A/S] was used for the detection. Sections were mounted and dehydrated after being counterstained with Mayer's hematoxylin. For every run, both positive and negative controls were employed. A positive control group of healthy human fallopian tube sections was employed. The primary antibody was not added to the corresponding regions to provide negative controls.

3.3. Assessment of the slides

Positive reactivity was evidenced by the presence of a brown end product at the antigen-specific sites. Two separate proficient pathologists, who remained unaware

of the diagnostic and clinical information, evaluated and scored the slides for staining intensity and proportionality index for Periostin-positivity. 0 represents negative staining, 1 indicates mild positivity (+), 2 indicates moderate positivity (++), and 3 indicates strong positive (+++). A positive score of 0 meant less than 5%, 1 meant between 5 and 25%, 2 meant between 26 and 50%, and 3 meant more than 50% on the proportionality index. A total score was obtained by adding the individual scores.

3.4. Statistical Analysis

All statistical analyses were performed using standard statistical software (IBM SPSS version 26.0). The periostin expression scores (combined intensity and proportionality index) were treated as ordinal data and summarized as mean ± standard deviation (SD). Intergroup comparisons were performed using the

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Kruskal–Wallis test followed by post hoc Dunn's test for pairwise comparisons. A p-value < 0.05 was considered statistically significant.

4. Results

Normal bone samples (n = 5) showed limited expression of periostin, mostly localized to the periosteal collagenous connective tissue, and with a low average expression score (0.4 ± 0.2). Conversely, all pathological groups had much higher periostin expression, such as fibrous dysplasia (2.7 ± 0.5), osteoma (2.6 ± 0.5), osteosarcoma (1.8 ± 0.6), and Paget disease (1.1 ± 0.4), whereas osteomyelitis exhibited minimal expression (0.2 ± 0.1) (Table 1) (Figure 1).The Kruskal-Wallis test with post hoc tests showed that the periostin expression in normal bone was significantly lower than fibrous dysplasia and osteoma ($p < 0.001$), osteosarcoma ($p < 0.01$), and Paget's disease ($p < 0.05$), and no significant difference was found in comparison to osteomyelitis ($p > 0.05$) (Figure 2).

Histologically, periostin was limited to extracellular collagenous areas, especially at tendon and ligament attachment sites in normal bone. Osteocytes, osteoblasts, and osteoclasts were uniformly negative, confirming its extracellular localisation to the matrix. The significantly increased expression in neoplastic and fibro-osseous lesions underscores its involvement in osteoid formation, stromal activity, and pathological bone remodelling, as compared to its insignificant contribution to normal bone homeostasis (Figure 3).

Table 1: Summary of IHC Results for Periostin Expression.

Diagnosis	No. of cases	Periostin Positive cases (%)	Mean Score (Mean± SD)
Osteosarcoma	10	45%	1.8 ± 0.6
Fibrous Dysplasia	10	95%	2.7 ± 0.5
Osteoma	10	95%	2.6 ± 0.5
Paget's disease	10	20%	1.1 ± 0.4
Osteomyelitis	10	0%	0.2 ± 0.1

Figure 1: Bar chart representing mean periostin expression scores. The mean periostin expression is highest in fibrous dysplasia and osteoma, followed by osteosarcoma, with minimal expression in Paget's disease and absence in osteomyelitis

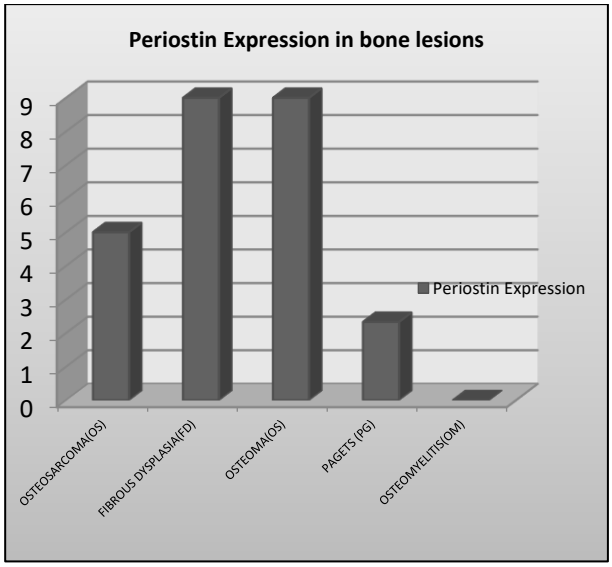

Figure 2: Box plot of periostin expression scores across different jaw lesions. The plot demonstrates the distribution, median, and variability of periostin expression among osteosarcoma, fibrous dysplasia, osteoma, Paget's disease, and osteomyelitis. Higher median scores are observed in fibrous dysplasia and osteoma, while osteomyelitis shows negligible expression.

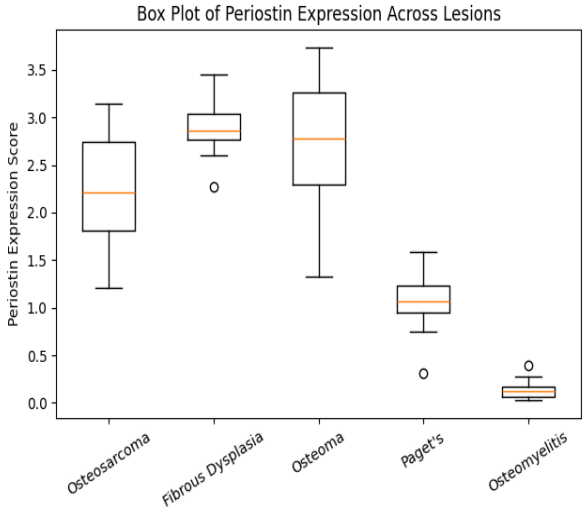

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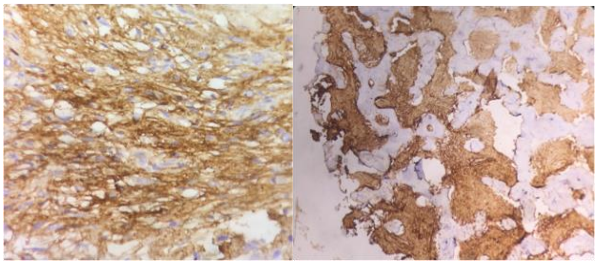
Figure 3: Immunohistochemical image demonstrating (1a) periostin expression in the extracellular matrix located between tumor cells of osteosarcoma. (1b) robust periostin staining in fibrous dysplasia, primarily localized within the cellular fibrous stroma surrounding bone trabeculae.



5. Discussion

Differential expression of periostin in distinct jaw bone lesions was clarified in the study, which suggested a possible role for this protein in both cancerous and non-cancerous bone diseases. The robust expression of periostin in osteoid/woven bone of neoplastic lesions, including osteosarcoma, highlights its significance in remodeling the tumor microenvironment and osteogenic processes. Periostin's prominent presence in fibrous dysplasia further suggests its role in the dysregulated production of bone matrix that characterizes this benign bone disease.

All of the fibrous dysplasia cases showed positivity for periostin. Periostin was localized to the cellular fibrous component of fibrous dysplasia. Other immunohistochemical and in situ hybridization studies has revealed the same results [9]. Since studies have shown expression of Periostin by primitive mesenchymal stem cells [10], we can speculate the role of the Protein in maintaining the primitiveness of the fibrous dysplasia and in not allowing it to ossify into a mature bone.

In a previous study by Lemaire HG et al [11], it was observed that serum periostin levels exhibited elevation in patients diagnosed with fibrous dysplasia (FD) compared to their healthy counterparts, particularly among those presenting with fractures, polyostotic forms, or McCune-Albright syndrome. Interestingly, no significant correlation was found between high pain levels and periostin levels. Notably, patients undergoing bisphosphonate therapy demonstrated lower periostin levels in comparison to treatment-naïve individuals. According to these results, periostin may be a useful biomarker for determining the severity of fibrous dysplasia and may hold promise as a monitoring tool for patients receiving bisphosphonate treatment.

Interestingly, the study also highlights the robust staining of periostin in reactive bone at the periphery of expanding tumors. This observation implies a dynamic interplay between periostin expression and the tumor microenvironment, particularly in regions of heightened vascularity and fibrosis. Such findings resonate with the emerging understanding of periostin as a modulator of angiogenesis and fibrogenesis[12], implicating its multifaceted role in tumor progression and stromal remodeling within the jaw bone. Periostin stimulates mesenchymal stem cell development into osteoblasts, which results in the synthesis of bone matrix, and boosts ECM production by fibroblasts and myofibroblasts[12][13]. It is known that periostin enhances osteoblast function and bone formation by acting as a signaling molecule through integrin receptors and WNT-β-catenin pathways[14].

The consistent presence of periostin in all osteoma cases underscores its integral role in bone formation via intramembranous ossification, akin to the physiological process beneath the periosteum [15]. This strong periostin expression in fibrous dysplasia and osteoma highlights its involvement in woven bone formation, accentuating its potential as a diagnostic marker and therapeutic target.

There have been reports of periostin expression in osteosarcoma before, and high expression has been linked to tumor angiogenesis and a bad prognosis. Around growing tumors, both benign and malignant, periostin was often expressed in the smooth muscle wall of tiny blood arteries located within non-lesional bone [16]. Vascular endothelial growth factor (VEGF) and its receptors interact with periostin is assumed to be important for both healthy and pathological angiogenesis.

The absence of periostin expression in osteomyelitis cases contrasts with its known presence in locations of inflammation, healing, and damage. This finding suggests a nuanced role for periostin in bone pathologies, wherein its absence in osteomyelitis may reflect distinct pathophysiological mechanisms. Periostin has also been shown as a key regulator in rheumatoid arthritis and osteoarthritis, highlighting its potential relevance in

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inflammatory bone conditions, urging further exploration of its involvement in the pathogenesis and management of osteomyelitis [17].

Thus, the observed variation in periostin expression across different bone lesions raises the possibility of targeted treatment effects. It may be possible to mitigate bone resorption, promote osteogenesis, and even impede tumor progression with pharmacological agents that modulate periostin expression or activity. The potential for targeting periostin in osteosarcoma and fibrous dysplasia as a therapeutic approach to disrupt tumor-stroma interactions and slow down the evolution of the disease is highlighted by the significant staining of periostin in these lesions.

Future research should explore the precise molecular mechanisms underlying periostin's role in bone pathophysiology and its interactions with other signaling pathways. Longitudinal studies should also investigate its correlation with clinical outcomes and treatment responses. This could lead to personalized medicine and improved patient care in maxillofacial pathology.

4. Conclusion

Overall, the study examines the expression pattern of periostin in different jaw bone lesions and demonstrates its possible diagnostic and prognostic value. Both cancerous and non-cancerous tumors, such as fibrous dysplasia and osteosarcoma, exhibit strong expression, whereas patients with osteomyelitis lack it, indicating alternative pathophysiological processes. Additional studies are required to learn the impact of periostin in bone lesions and its clinical use in personalized medicine.

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