LETTER to the EDITOR

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Incessant Role of Fibroblast in Malignant Transformation of Gnathic Fibro-Osseous Lesions? – Should We Rework on Treatment Strategies

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Dear Editor

Malignant transformation in gnathic fibro osseous lesions (GFOL) is still a matter of debate. Gnathic fibro-osseous lesions undergo a myriad of developmental, dysplastic and neoplastic alterations characterized by the replacement of bone by cellular fibrous connective tissue with varied amount of mineralized tissue. Pathogenesis of these lesions are still ambiguous considering its propensity to occur in a multitude of extraoral sites (Rabelo et al., 2020). "Hypercellular fibroblastic stroma" is the key histopathologic feature in GFOL, wherein activated fibroblasts have a serious impact on a multitude of tissue homeostatic mechanisms like immune cell chemotaxis, infiltration, trans endothelial migration, retention, and apoptosis, and underlying mechanisms (McCarthy EF, 2013). We emphasize that these facts need to be contemplated so as to decode pathogenesis and to derive a comprehensive therapeutic regime for effective management of these enigmatic lesions.

Role of Dysregulated multipotent fibroblast cells in pathogenesis of GFOL

Fibroblasts exhibit intricate crosstalk between components of innate and adaptive immunity modulating the tissue microenvironment. Their overwhelming demeanour abrogates the current treatment strategies targeting inflammation alone (Linthout, 2014). The colossal transformation that it endows is a matter of serious concern principally due to possibility of a spectra of changes ranging from aberrant proliferation to neoplastic transformation.

Fibroblasts derived from periodontium exhibit significantly higher bone remodeling activity than alveolar bone. In healthy states, the cell turnover is balanced and highly ordered due to instructive and permissive signaling and cytodifferentiation. However, this immense vitality is deranged in the presence of ubiquitous inflammation with poor oral hygiene. Inflammation and immunological reactions trigger a series of cellular responses, specifically the fibroblasts. They are a heterogeneous population of stromal cells in the periodontium that emerge from an unfathomable epithelium and mesenchymal transition.

Whether the osteogenic (bone/cementum) phenotype expression is augmented in fibroblasts of GFOL?

GFOL are mostly derived from fibroblasts of periodontal origin than fibro-osseous lesions of medullary bone origin. Periodontium has multipotent mesenchymal blastic cells capable of forming cementum, alveolar bone and fibrous tissue. Neoplastic disorder results in cementum, lamellar bone, fibrous tissue or a combination of this spectra. Severity of GFOL than other lesions can be attributed to the dysbiotic microbiome present in diseased periodontium. Neoplastically altered fibroblasts are proven to be alarming, additionally the chronic microbial onslaught exacerbates the activation. Fibroblast in fibrous dysplasia or ossifying fibroma take up the osteoblastic phenotype either by missense mutation in GNAS or CDC73 leading to the genesis of osteosarcoma over the years.

Indicative histologic & molecular events that needs to be reminisced during diagnosis and treatment planning

Gnathic fibroosseous lesions present a diverse spectrum of histopathologic features than FOL arising in other sites of the body. Tissue changes range from mesenchymal proliferations exhibiting reactive to neoplastic features. Precise monitoring of fibroblast morphology is vital in diagnosis of GFOL. Phenotypical changes in cell shape, cytoplasm and nucleus have to be scrutinized in depth for features of high cellular activity, stellate shape or spindle cell morphology, autophagic vacuoles, undulating membrane and multiple processes. Additionally defining the immunophenotype with markers α-smooth muscle actin, Fibroblast specific protein-1 suggestive of transdifferentiation are crucial in diagnosis. Furthermore the matrix components needs to analysed for presence of non-collagenous proteins which commonly exhibit varying degree of high alkaline phosphatase activity (Hameed et al., 2020).

Molecular alterations pertaining to fibroblasts need to be given more thrust as scientific advances are more denotive of their potent immunomodulatory properties. Mutation in GNAS or CDC73 that occur in fibrous dysplasia is also noted in osteosarcoma following Fibrous Dysplasia (Hameed et al., 2020). Immunoexpression of CDC73/parafibromin have been demonstrated in the blastic cells of Ossifying fibromas of the familial hyperparathyroidism jaw-tumor syndrome and in the blastic cells of Osteosarcoma. This fact evinces the role of incomplete migration of multipotent mesenchymal blastic cells in histogenesis of the lesion in areas other than jaw. Comparable aggressive behaviour is also exhibited in

fibromatosis which exhibit transdifferentiation resulting from an aberrant healing pathway. Other molecular include up-regulation of SDF/CXCR4,MDM2, RASAL1 and CDK4 amplification should also be considered even in benign appearing lesions (Cleven, 2020; Hameed et al, 2020).

In conclusion, Surgical reshaping happens to be the mainstay of treatment in GFOL. Pharmacotherapy with steroids, calcitonin and pamidronate is used only as an adjunctive option to provide symptomatic relief. In view of dysregulated fibroblast in GFOL, histopathological and morphological changes needs to be closely monitored as they exhibit unprecedented behavior leading to malignant transformation. Thus, specific targeting of accelerated fibroblasts with therapies such as immunoconjugates, tumor immunotherapy, CAR T cells, peptide drug complexes, FAP (Fibroblast Activation Protein) inhibitors and antibodies should be considered in management of GFOL.

References

Cleven AHG, Schreuder WH, Groen E, Kroon HM, Baumhoer D (2020). Molecular findings in maxillofacial bone tumours and its diagnostic value. *Virchows Arch*, **476**, 159-74.

Hameed M, Horvai AE, Jordan RCK (2020). Soft Tissue Special Issue: Gnathic Fibro-Osseous Lesions and Osteosarcoma. *Head Neck Pathol*, **14**, 70-82.

Linthout SV, Miteva K, Tschöpe C (2014). Crosstalk between fibroblasts and inflammatory cells. *Cardiovascular Res*, **102**, 258–69

McCarthy EF (2013). Fibro-osseous lesions of the maxillofacial bones. *Head Neck Pathol*, **7**, 5-10.

Rabelo N, Silva VTG, Santo MPE, et al (2020). Orbit ossifying fibroma - Case report and literature review. *Surg Neurol Int*, **11**, 1-6.

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