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Role of Glycosaminoglycans and Matrix Metalloproteinases in Aggressive Behavior of Myxomas: a Review with Report of Two Cases of Odontogenic Myxoma of Anterior Jaws

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ABSTRACT

Myxomas are soft tissue benign neoplasms commonly associated with Carney's Complex as cardio-cutaneous myxomas. Odontogenic myxoma is a rare variant occurring in head neck region and is considered to be originated from ectomesenchymal portion of developing tooth germ. It is a slow growing non metastasizing tumour exclusively seen in jaw bones but may also be present in other soft tissues of oral cavity. It shows a locally invasive biological behavior which results may results in marked facial asymmetry**.** Histochemical analysis of myxomas has abundance of Glycosaminoglycans which are thought to be responsible for their aggressive behavior. The glycosaminoglycans present in Odontogenic Myxoma can be identified and quantified using Immunohistochemical and histochemical methods respectively. Here we report two cases of Odontogenic Myxomas showing dissimilar clinical presentations with respect to gender, age, size and site and a review on the histochemical composition of myxomatous tissue and its possible role in its biological behavior.

Key-words: Odontogenic Myxoma, infiltrative nature, histochemical analysis, Glycosaminoglycans, Matrix metalloproteinases

INTRODUCTION

R. Virchow introduced the term "Myxoma" for soft tissue tumours of mesenchymal origin with stark resemblance to primitive mucoid tissue of umbilical cord. [1] Myxomas are rare benign locally invasive tumours. Goldman and Thoma in 1947 introduced a rare variant of Myxoma occurring in head and neck region and called it as "Odontogenic Myxoma". [2] Odontogenic myxoma comprises of 3% to 6% of all odontogenic tumours. It mostly seems to involve lower jaw of females in 2nd to 3rd decade of life. Simon et al. reported only 4% of all lesions crossing the midline. This tumour is slow growing expansile in nature with cortical expansion/destruction and regional root displacement. Large lesions lead to facial asymmetry. [3] Radiographically it presents as a unilocular or multilocular radiolucent lesion with well-defined borders within the jaws. Unilocular lesions were commonly seen in anterior while multilocular lesions in posterior jaws. Friedrich et al. reported only 25% cases representing as multilocular lesions. In 50% of cases multilocular lesions form fine trabeculations giving a characteristic "Honey comb" appearance. [4]

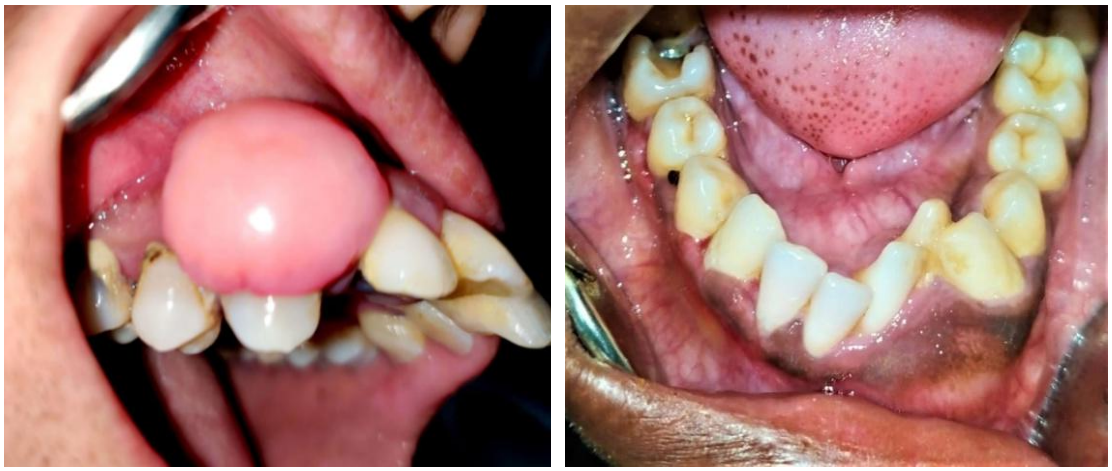
Biological behaviour of Myxomas remains a paradox. Although slow growing, this tumour becomes quite aggressive. Malignant variant of Myxoma called Myxosarcoma is quite infrequent. [5]

Slootweg et al. proposed aggressive behaviour of Myxoma related to their extracellular matrix containing Glycosaminoglycans. Glycosaminoglycans are found in abundant quantity in ground substances of myxomas. Hyaluronic acid and Chondroitin Sulphate are the integral component of these Glycosaminoglycans. [6]

Two cases of odontogenic myxomas which acquired a large size in a short period of time have been reported hereby. An attempt has been made to describe the components of the ground substance of myxomatous tissue, its histogenesis and possible role in aggressive behaviour of Odontogenic Myxoma.

CASE REPORTS

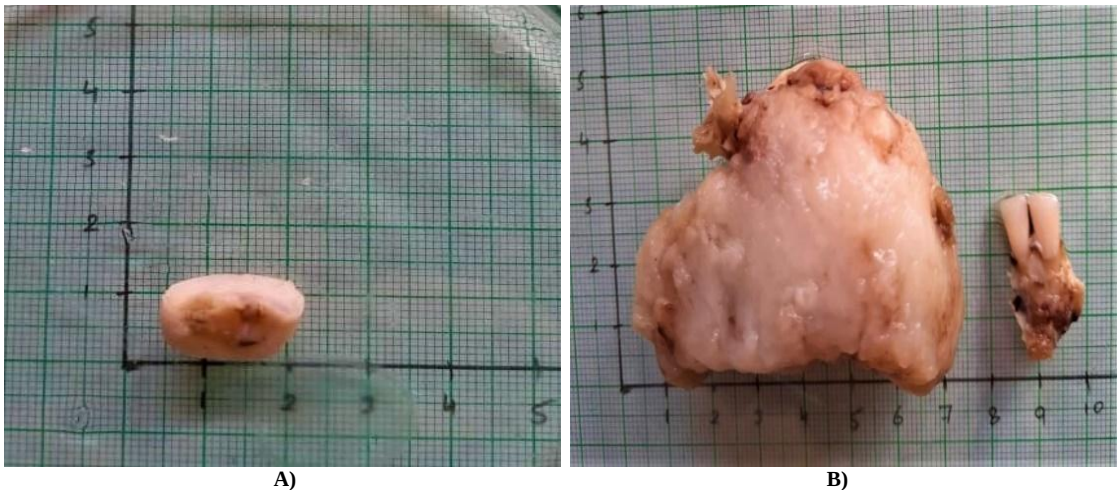
Case 1: A 48 year old female reported with complain of fast growing swelling in right anterior maxilla since 3 months. Clinical examination revealed a well-defined sessile smooth surfaced growth measuring approximately 3cm x 5cm in diameter in relation to #12 to #14 (figure 1A). Gross excisional tissue was round, smooth textured and firm in consistency (figure 1B).



A) **B)**

Figure 1: A) Intra oral photograph of case 1 showing swelling in right maxilla B) Intraoral photograph of case 2 showing swelling of anterior mandible

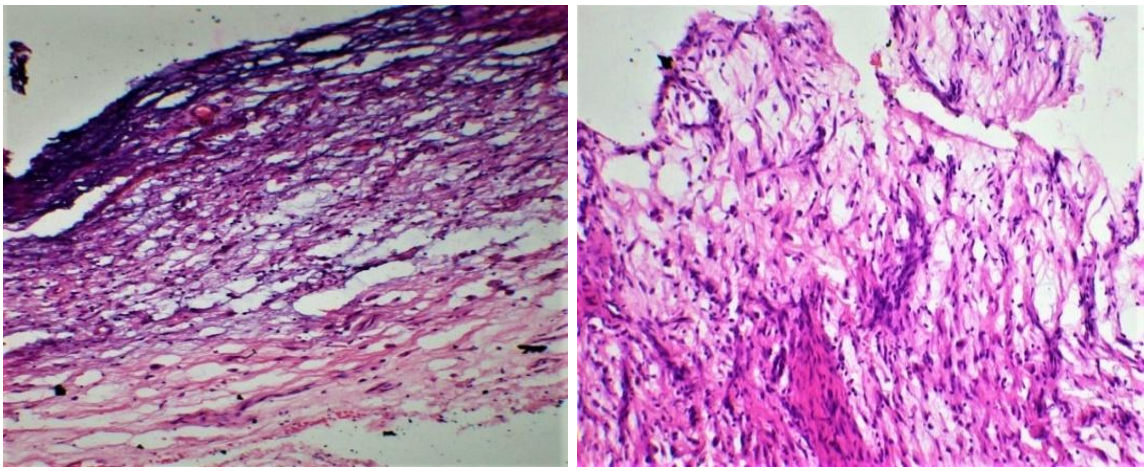
Case 2: A 25 year old male reported with complain of swelling in anterior mandible since one year. Clinical examination revealed slow growing progressive swelling approx. 5cm x 3cm x 3cm extending from #34 to #45 with obliteration of labial vestibule and mobility, displacement of regional teeth (figure 1B). Gross excisional specimen showed a yellowish white hue mass with gelatinous, glistening, smooth textured surface (figure 2B).



A) **B)**

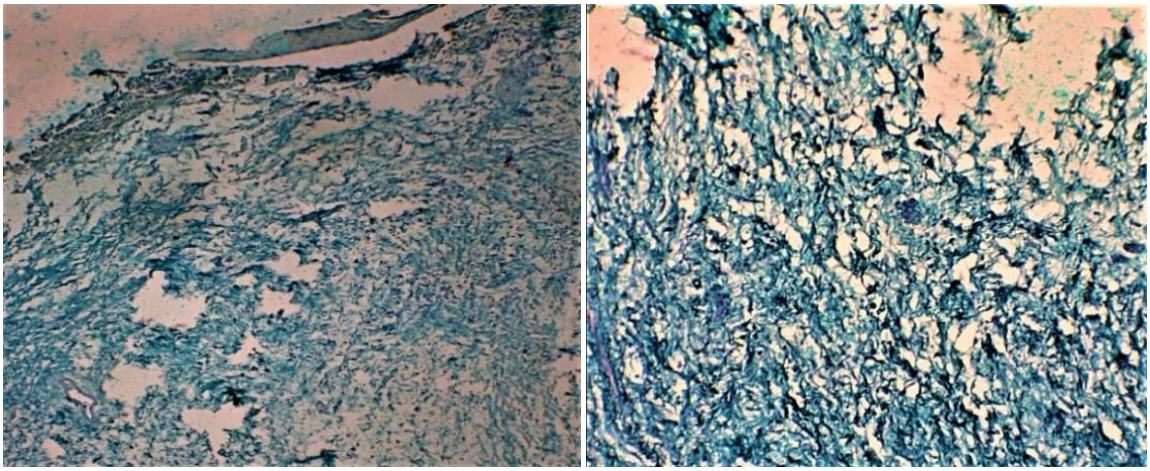
Figure 2: gross excisional biopsy specimen of A) case-1 B) case-2 showing glistening gelatinous surface

Histopathologically both cases revealed plump active spindle or angular shaped mesenchymal cells with long anastomosing processes scattered haphazardly in a mucoid background with collagen fibres. Odontogenic epithelial rest were noted**.** Few interspersed fine capillaries were seen. Stroma consist of abundance of ground substance and moderate inflammatory cell infiltration (figure 3A and 3B). Strong positive staining with Alcian Blue was noted depicting the abundance of GAGs (figure 4A and 4B).



A) **B)**

Figure 3: Photomicrograph of Case-1 (A) and Case-2 (B) showing presence of loosely arranged spindle or angular cells in an abundant myxomatous background in H & E section



A) **B)**

Figure 4: strong positive Alcian Blue staining depicting the presence of glycosaminoglycans in ground substance of Case-1 (A) and Case-2 (B)

DISCUSSION

The connective tissue of the umbilical cord also called as "Wharton's jelly" is a derivative of extraembryonic mesoblast and composed of ground substance containing polysaccharides, mainly Hyaluronic Acid. [7] Histochemical analysis of ground substance of myxomas reveal similar composition. Hodson and Prout proposed the concept of "myxoblast" for cells continuously secreting Hyaluronic Acid. [8] According to Willis this tumour exhibit myxomatous degeneration of connective tissue tumour like fibroma, angiomas or nerve sheath tumours. Based on their histological presentation, Stout called Myxomas as true mesenchymal neoplasm. [9]

Origin of Odontogenic myxoma has been proposed based on its exclusive site of tooth bearing areas, its occasional association with impacted or missing teeth

and the presence of odontogenic epithelial rests. [3] The genetic association of this mesenchymal tumour has been attributed to genetic aberrations. Mutation of GNS alpha-1 gene regulating GTPase activity and PRKR1A gene involved in regulation of cAMP dependant protein kinase-A is thought to be associated with cardio-cutaneous myxomas and few odontogenic myxomas. [5]

Histology

Microscopic picture of Myxoma reveals characteristic plump active branching "stellate, spindle or angular" shaped cells scattered in network pattern in a loose eosinophilic stroma comprising of abundant Glycosaminoglycans, numerous reticulin fibres and thin calibered vessels resembling the primitive connective tissue. The abundance of mucoid stroma can be attributed towards their aggressive or infiltrative behaviour. [3] Presence of Epithelial islands is infrequent but Lombardi et al. and Muzio et al. reported presence of epithelial islands in 15% to 20% cases respectively.

Special Stains

Glycosaminoglycans can be carboxylated (hyaluronic acid) or sulphated (chondroitin sulphate 4 and 6) and they get ionized at different pH. The contents of GAGs in myxomatous tissue can be confirmed with special stains. Scott used a cationic dye Alcian Blue with varying pH to demonstrate the presence of different Glycosaminoglycans. In Scott's technique, only sulphated GAGs are ionized at lower pH of 1.0 while both Carboxylated and Sulphated GAGs are ionized at pH 2.5. [11] This ionizing property at different pH is useful in differentiating Chondroitin sulphate and Hyaluronic Acid.

Beside Alcian Blue, Kindblom et al. used Toluidine Blue dye to demonstrate the presence of Hyaluronic Acid and Chondroitin Sulphate. Hyaluronic Acid showed metachromasia at pH 4.0 and Chondroitin Sulphate at pH 0.5. Quantitative estimation of these mucosubstances is possible by grading the intensity of staining. [8] Consistent presence of copious amount of these GAGs seems to play a vital role in determining the biological behaviour of Odontogenic myxoma.

Immunohistochemistry

These tumours show positive staining for vimentin and S-100 marker indicating their mesenchymal origin. M Zhao et al. demonstrated the presence of Chondroitin Sulphate 4 and 6, Keratin Sulphate and Dermatan Sulphate using monoclonal antibodies with more than 80% positively stained matrix area. Hyaluronic Acid detection was done using biotinylated HA binding protein. Hyaluronic acid has been a constant component found in the ground substance of Odontogenic myxoma. [8]

Histochemistry

Histochemical analysis of Odontogenic Myxoma reveals presence of high concentration of Glycosaminoglycans chiefly Hyaluronic Acid and Chondroitin sulphate in a ratio of 4:1. [1] Quantitative analysis of jaw Myxoma by Hodson and Prout demonstrated 80% of mucopolysaccharides consist of Hyaluronic Acid. Histochemical analysis of Odontogenic Myxoma by M. Zhao et al. showed presence of hyaluronic Acid and Chondroitin sulphate which was comparable to dental papilla tissue. [8]

Role of Glycosaminoglycans (GAGs) and MMPs in tumour behaviour:

Glycosaminoglycans in Odontogenic Myxoma

Different types of Glycosaminoglycans present in ECM of Myxoma are Hyaluronic acid, Chondroitin sulphate, Keratin sulphate, Dermatan sulphate, heparin sulphate and Heparin. Van Den Boss found higher concentration of chondroitin sulphate, Dermatan sulphate and keratin sulphate in Myxomas.

Histochemically identified mucopoly-saccharides are collectively called as "Heteroglycans," which includes the glycosaminoglycans (keratan sulphate, sialo glycan) and the glycosaminoglycans conjugated with Glucuronic acid (hyaluronic acid, chondroitin 4- and 6-sulphate, dermatan sulphate, and heparin). [6] All these heteroglycans carries a negative charge due to the existence of sulphate and carboxyl groups and get precipitated by a cationic dye. Kindblom et al. revealed the occurrence of Glycosaminoglycans in large amount in Wharton's jelly and neoplastic myxoid tissues. Glycosaminoglycans are heteropolysaccharides widely distributed in mammalian tissues and are formed of polysaccharide chains also called as mucopolysaccharides. Hyaluronic acid is not sulphated and may be found freely in tissues, but all the other Glycosaminoglycans are linked covalently to proteins and form proteoglycans. [8]

Hyaluronic Acid

It is the simplest Glycosaminoglycan in ECM of mesenchymal tissue. High concentration of Hyaluronic acid may correlate with tumor aggressiveness. Hyaluronic acid absorbs water and causes tissue expansion, create pathways for tumour cell movement and metastasis. [6] Collaboration of Hyaluronic Acid with surface receptors of tumour cells augments tumor cell survival and invasiveness. Hyaluronic Acid acts as a space filler, promotion of cell migration, regulator of cell cycle, ion exchange filter between surrounding tissue and fluid, embryonic development, tissue repair and regeneration. Beside these, it is also involved in inflammation, angiogenesis and wound healing. [12]

Chondroitin Sulphate

Chondroitin Sulphate is also a constant component of myxomatous tumours. Chondroitin sulphate has been richly found in ECM of myxoid Chondrosarcoma and myxofibrosarcoma, chiefly Chondroitin Sulphate 4 and 6. The normal function of Chondroitin Sulphate has been implicated in cell proliferation, migration and inhibition of apoptosis via interacting with Fibronectin and Tenascin. [6]

Versican

Versican is a Chondroitin Sulphate proteoglycan which stimulates the fibroblast proliferation. Its expression is increased in rapidly dividing cells of myxoid tissues. Versican is a central player in cancer development and its expression increases as a part of inflammatory response. [13] Yumi Ito et al. in a study demonstrated the localization of versican in epithelium and connective tissue of odontogenic tumours like Ameloblastoma, AOT, CEOT and OKC. Based on the presence of abundant quantity of versican, they tried to explain the expanding and infiltrative nature of these Odontogenic tumours. [14] Immunohistochemical study by M. Zhao et al. also demonstrated positive immuno-staining for versican in Odontogenic Myxomas. [8]

Matrix metalloproteinases involved in aggressive behaviour of Odontogenic Myxoma:

MMPs are biological enzymes produced by various connective tissue cells including osteoblast, fibroblast and odontoblasts. One of the known function of MMPs is to hydrolyse the components of ECM, thereby facilitating the process of infiltration by tissue remodelling and regulation of growth factors, cytokine and adhesion molecules. Randall and Hall in their histochemical analysis identified the presence of MMP-1, 2, 3, and 9 during bud stage of tooth development. They also suggested the role of MMP-9 in degradation of basement membrane. [5] Miagi et al. in their study demonstrated the presence of MMP-2 and MMP-9 in Odontogenic myxomas. These MMPs are thought to be involved in the hydrolysis and disintegration of bony trabeculae and may play a crucial

role in aggressive and infiltrative behaviour of Odontogenic Myxomas. [15]

CONCLUSION

Odontogenic myxoma is a locally aggressive benign tumour with fairly good prognosis but shows a high recurrence rate. We have discussed the aggressive nature of this tumour based on its histochemical composition. The Extracellular Matrix of Odontogenic Myxoma histologically and histochemically appears identical to the primitive connective tissue showing presence of abundant Glycosaminoglycans. The Infiltrative nature of these tumours has been associated with the presence of high concentration of Glycosaminoglycans in its stroma.

We propose that laboratory studies in terms of identification, quantification and assessment of composition of myxomatous tissue may help in understanding of its biological behaviour and will provide a base for better therapeutic strategies to prevent recurrence.

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