Review Article

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Histogenetic Concepts, Terminology and Categorization of Biphasic Tumours of the Oral and Maxillofacial Region

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ABSTRACT

A biphasic tumour is a truly histological term that refers to neoplastic tissue which is characterized by two different cellular elements. Several histogenetic theories have been proposed for the aetiogenesis of the biphasic tumours. Literatures have been published on the individual lesions, which have described their biphasic nature but, biphasic tumours have not been categorized singly . Categorizing biphasic tumours is not likely to highlight diagnostic standards, but it may sensitize the therapeutic planning and post operative monitoring. This review article focuses on the histogenetic concepts of biphasic tumours, and the histopathological description of the lesions that are suggested to be biphasic tumours.

Keywords: Biphasic, Bimorphic, Histogenetic concepts, Synovial sarcoma, Epithelial-myoepithelial carcinoma

INTRODUCTION

Willis defined the term, 'neoplasia' as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change [1]. Initially, neoplasias were considered to be monoclonal in origin; the modern concept of cancer suggests that as the tumour progresses, it becomes polyclonal, making cancer treatment a difficult task [2]. The origin of cancer is considered to arise from normal stem / progenitor cells. The reason that a successful tumour initiation occurs in normal adult stem/progenitor cells, is that normal cells have a self-renewal mechanism in place that allows their longevity, and that there is a system that continuously renews their cell population, i.e., the haematopoietic system. Further, once cells leave the stem cell niche, they are destined for efflux from the system, and can undergo multiple somatic mutations which are required for formation of a malignancy [3]. The mechanism of Epithelial Mesenchymal interactions has been poorly understood, but it is known that fibroblasts can accelerate the growth of epithelial cells and that keratinocyte growth factor may be responsible for this fibroblast- epithelial interaction [4]. Although a tumour causes the proliferation of transformed/mutant cells, the proliferation of adjacent stromal cells has also been observed. Microscopic inspection of most of the tumours reveals a complex heterogenous picture. Phenotypic and behavioural cell heterogenicity is generated in part by the variation which occurs within a tumour, with respect to its proximity to the vascular network and because not all of the cells are cancer cells. Non-cancer cells which are found within a tumour include: inflammatory cells, cancer associated fibroblasts and immature myeloid cells, all of which influence tumour behaviour and which often facilitate tumour invasion and metastasis. The microenvironment which surrounds blood vessels represents the source of the highest rates of tumour cell proliferation and it regulates cancer stem cells [5].

There is a suggestion that tumours be characterized by co-proliferation of epithelial and mesenchymal elements. The stromal proliferation is considered to be a non-neoplastic proliferation generally, as often these proliferated stromal cells may appear to be equal in number as malignant tumour cells. This gives the appearance of a two-cell population in the malignant tissue, and hence the lesions are termed as biphasic tumours. The term, "biphase" implies two different phases, and it supports the fact that the origin of the tumour is from two different cells. However, the term, 'biphasic tumours' can be used in conditions where tumour tissue is characterized by two different cell populations and where both cell populations demonstrate a malignant nature microscopically. In contrast, the tumour tissue that is characterized by two different cell populations and is of a malignant nature, that is observed with one cell population, is termed as a bimorphic tumour. In bimorphic tumours, the tissue is characterized by proliferation of two different cell populations, one being neoplastic and one which has a non-neoplastic proliferation.

This review will focus on the histogenetic concepts of biphasic tumours and the histological appearances of biphasic tumours of the jaw and it will therefore include Spindle Cell Carcinoma (SPCC), Nasopharyngeal Carcinoma – undifferentiated type (NPC), Synovial Sarcoma (SC), Carcinosarcoma Of Salivary Gland (CSSG), Melanotic Neuroectodermal Tumour of Infancy (MNTI), Epithelial-Myoepithelial Carcinoma (EMC) and Mesenchymal Chondrosarcoma (MCHS). The tumours that histologically mimic biphasic tumours of the jaw, Myofibroblastoma (MF) and Neurilemmoma (NL) have also been discussed.

Histogenetic Concepts

There are four main histogenetic concepts that have been proposed to explain the biphasic nature of tumours. (1) The Collision Theory suggests that the carcinomatous and sarcomatous elements are two independent neoplasms. (2) The Combination Theory suggests that both components are derived from a single stem cell that undergoes a divergent differentiation early in the evolution of the tumour. (3) The Conversion Theory suggests that the sarcomatous element derives from the carcinoma during the evolution of the tumour. (4) The Composition Theory suggests that the spindle cell component is a pseudosarcomatous stromal reaction to the presence of the carcinoma [6,7] [Table/Fig-1].

Spindle Cell Carcinoma

Spindle cell carcinoma is a variant of squamous cell carcinoma. Four theories have been proposed to explain the histogenetic concept of spindle cell carcinoma. The first theory suggested that the spindle cells and epithelial cells arose simultaneously from separate stem

Concepts of biphasic tumor	Reference
Lineage restricted clonality in bhasic tumors.	[4]
Collision, Combination, conversion and Composition theories of biphasic tumors	[6]
Divergent histogenesis theory of Carcinosarcomas	[7]
Tumorigenesis in Nasopharyngeal carcinomas	[8]
Biphasic nature in Epithelial myoepithelial Carcinoma	[9]
Two cell types in Mesenchymal Chondrosarcoma	[10]
Biphasic populations in Melanotic Neuroectodermal Tumor of Infancy	[11]
Mimicking biphasic natue of myofibroblastomas	[12,13]
Biphasic pattern of Neurilemmoma	[14]

[Table/Fig-1]: Concepts of biphasic tumors in Oral and Maxillofacial Region

cells and the name, "Collision Tumour" was proposed. The second theory explained that the nature of the spindle cell component was an atypical reactive proliferation of the stroma and the name, "pseudosarcoma" was proposed. This theory supported the Composition theory. The third theory explained that both the spindle and epithelial components had the same monoclonal origin, and that transformation to spindle cells had occurred in the later stages, due to the "driving force" of the malignant epithelial cell. This supported the Conversion theory of biphasic tumours. The fourth theory explained that the spindle component was caused by the de-differentiation of the tumour cells [15,16]. Immunohsitochemical studies suggested that some of the spindles that had a mesenchymal appearance expressed dual antigen-positivity with both cytokeratin and vimentin markers [17].

Microscopically, the tumour is characterized by a dysplastic epithelium and spindle cells in the stromal tissue. Most often the overlying epithelium shows ulceration. The tumour is considered to be biphasic or bimorphic, as it shows a dysplastic epithelium and spindle cells in connective tissue stroma. The gradual transition of the dysplastic epithelium to the spindle cell element at the basal cell layer is described as the "dropping-off" phenomenon. The cells in the connective tissue stroma are categorized as fasiculated or streaming fashion. The cells in fascicles are elongated and they have elliptical nuclei. Mitotic figures which are observed may range between few to many [18]. The presence of the giant cells in the lesional tissue was also reported. Giant cells may be found in the tissue [19]. Osteoid formation may be seen sometimes**.** [20] Immunohistochemical studies showed that the spindle cell component of the carcinomatous tissue displayed dual antigen positivity for epithelial and mesenchymal elements such as cytokeratin and vimentin. The dual antigen positivity suggests that the cells are in transition and it may represent sarcomatous metaplasia of a squamous cell carcinoma [17].

Nasopharyngeal Carcinoma (undifferentiated type)

This tumour represents a malignant tumour of the lining epithelium of the nasopharynx. Microscopically, these tumours can be recognized to be of three types, based on the keratinizing character of the tumour tissue: Well differentiated squamous cell carcinoma, keratizing carcinoma and undifferentiated carcinoma [21]. Microscopically, the tumour is characterized by solid sheets of syncytial appearing, large tumour cells which are arranged in irregular islands. The tumour cells show large vesicular nuclei and little / scanty cytoplasm. There is often a cellular overlap of tumour and inflammatory cells. The malignant epithelial cells are often seen as islands and well-defined islands are termed as the "Regaud pattern". In contrast, the individual malignant cells which are seen as ill-defined sheets are termed as the "Schminc pattern" [22]. The tumour cells are intermingled with inflammatory elements. Due to the dominant lymphoid component in the tumour tissue, it was assumed that the tumour originated from both epithelial and lymphoid tissues and the name, "lymphoepithelioma" was proposed. However, lymphoid cell proliferation is non neoplastic [8]. Immunohistochemical studies done on undifferentiated nasopharyngeal carcinoma showed strong and diffuse immunoreactivity to cytokeratins 5 and 6. The lymphoid population is polytypic, with the presence of B and T cell markers. The tumour tissues that are intermingled with the lymphoid component show that the cytoplasm reacts with keratin to create a "meshwork pattern" [22]. Immunohistochemical studies also suggested cytoplasmic reactivity for cytokeratin and/ or epithelial membrane antigen [23]. In-situ hybridization studies have documented the presence of the Epstein Barr virus in undifferentiated nasopharyngeal carcinoma tissues. In contrast, differentiated / keratinized types of nasopharyngeal carcinomas do not show any evidence of the Epstein Barr virus in their tissue specimens. There is a strong association between Epstein Barr virus infections and the undifferentiated form of the tumour [24]. The prognosis and survival rate are considered to be poor in cases which show the undifferentiated form of the tumour [25]. Although the two different cell populations are frequently found in undifferentiated nasopharyngeal carcinomas, only the squamous cell population undergoes neoplastic transformation. Based on the histocharacterization of cellular population in undifferentiation nasopharyngeal carcinomas, the tumour can be termed as a bimorphic tumour [23].

Synovial Sarcoma

Synovial sarcoma represents a tumour arising from synovial tissue, that presents with both lining cells and subsynovial stromal cells [9]. It arises from the pleuripotential mesenchymal cells near joint surface, tendons, tendon sheaths, juxta-articular membranes and fascial aponeuroses [9]. It is a carcinosarcoma like tumour with a true epithelial differentiation and hence, it is named is a misnomer [26]. Microscopically, it is characterized by two strikingly well distinct cell populations: spindle cell elements (primary component) and an epitheloid (secondary) component. The spindle cells are long, slender and they exhibit little or no pleomorphism. The intervening stroma which is seen between each spindle cell is scant. A fibrosarcoma like pattern may be evident. However, a herringbone pattern is not prominent; the spindle cells tend to appear in various planes and in a nondescript arrangement. The spindle cells become plump, lose much of their spindle shape, and in extreme situations, they assume a distinct epithelial appearance. The numbers of mitotic figures vary. The epitheloid cells are large, polygonal shaped and they show an organization of microscopic joint spaces. These epitheloid cells are surrounded by spindle cells that simulate subsynovial mesenchymal cells. The epitheloid cells are less prominent than the spindle cells. The epitheloid cells tend to be oriented in slit/cleft like spaces; however, this feature is not a constant histocharacteristic [27]. Microscopically, two predominant types: mono and bimorphic forms of synovial sarcoma may be identified. Monomorphic cells show spindle cell component, whereas bimorphic cells show both spindle and epitheloid components [9,28,29]. Immunohistochemical analysis of epitheloid, spindle cells revealed positivity to cytokeratin and epithelial membrane antigen, but vimentin positivity was observed in spindle cells only [30-32]. Synovial sarcoma arises from primitive cells that have the potential to differentiate into either mesenchymal or epithelial components [27]. Based on the histogenetic origin of synovial sarcomas, the biphasic nature of the tumour is explained by using the combination theory.

Carcinosarcoma of Salivary Gland

Carcinosarcomas of salivary glands represent the malignant counterparts of pleomorphic adenomas or benign mixed tumours. They are considered to be true and high grade malignant mixed tumours in which both the epithelial and stromal components fulfill the histological criteria of malignancy and display its atypical features [33]. Two antithetical hypotheses have been proposed to explain the histogenesis of carcinosarcomas, namely the convergence and divergence hypotheses. The convergence hypothesis supports the

polyclonal nature of tumourigenesis and it suggests that origin of carcinosarcomas is from two or more stem cells. The divergence hypothesis supports the monoclonal nature of tumourigenesis and it suggests that origin of carcinosarcomas is from a single totipotential stem cell that differentiates into separate epithelial and mesenchymal components [7]. The divergence hypothesis supports the combination theory and convergence hypothesis supports conversion theory. The convergence theory explains that carcinamatous component is "driving force" and that sarcomatous component develops eventually during tumour progession, thus being a component of conversion theory [6]. Microscopically, the tumour tissue is characterized by the presence of both carcinamatous and sarcomatous elements of varying proportions and it suggests true biphasic nature of the tumour [34]. The carcinomatous component of the tumour may resemble a ductal adenocarcinoma or a squamous cell carcinoma. The sarcomatous component may be observed in the chondroid, osteoid or fibrous elements. It thus resembles chondrosarcomatous, osteosarcomatous or fibrosarcomatous areas. However, these tumours are predominantly of the chondrosarcomatous type [9, 35]. The tumour tissue may show the infiltration of malignant cells into nervous tissue [36].Immunohistochemical studies revealed the positivity for cytokeratin in carcinomatous cellular component. In contrast, the carcinomatous and sarcomatous cells showed some degree of immunoreactivity for vimentin and S100 protein [37,38]. Carcinosarcoma of salivary gland represents the malignant counterpart of a pleomorphic adenoma. Ultrastructrual studies have explained that the histogenesis of the pleomorphic adenoma is from myoepithelial cells and reserve cells in the intercalated duct [9]. Based on this explanation, it was suggested that myoepithelial cells possessed epithelial and mesenchymal components. The carcinomatous component of this myoepithelial originated tumour could drive the sarcomatous process and if so, it could support the Conversion Theory origin of the biphasic nature of this tumour.

Epithelial-Myoepithelial Carcinoma

The epithelial-myoepithelial carcinoma is a low grade malignant salivary gland tumour. Microscopically, it is characterized by solid lobules that are separated by bands of hyalinized fibrous tissue[9]. Most of the tumours show a multi-nodular growth pattern with islands of tumour cells that are separated by dense bands of fibrous connective tissue. The islands of tumour cells are composed of small ducts which are lined by cuboidal epithelium, which are surrounded by clear cells with a thickened basement membrane. The inner luminal cuboidal cells have a finely granular, dense cytoplasm. The outer clear cells may vary in shape from columnar to ovoid, with a vesicular nucleus, with the nucleus being located towards the basement membrane [39]. The biphasic appearance of epithelial-myoepithelial carcinoma is due to the presence of ductal lining cuboidal cells, which is an epithelial component, and clear cells. The histogenesis of the clear cells is that they originate from myoepithelial cells. The histocharacteristics of epithelial-myoepithelial carcinoma, and the expression patterns of both the epithelial and myoepithelial cells support the biphasic appearance of the tumour.

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a histological variant of a chondrosarcoma [9]. It is microscopically characterized by varying amounts of differentiated cartilage which are admixed with undifferentiated small round or ovoid cells [40]. The differentiated cartilagneous component is in an early stage of maturation and often, these islands show calcification and metaplastic bone formation [41]. Immunohistochemical studies done on mesenchymal chondrosarcomas showed S-100 positivity [42,43]. Few authors mentioned that S-100 helped in assessing chondrogenicity of human articular chondrocytes [44]. Ultrastructural studies demonstrated two cell types 1) poorly differentiated mesenchymal cells with a sparsity of organelles and 2) a cartilaginous differentiation with well-developed cell organelles [10]. Although a two cellular population is observed in mesenchymal chondrosarcomas, both cell populations are derived from a single cell lineage and this supports the Combination Theory explanation for the biphasic nature of this tumour.

Melanotic Neuroectodermal Tumour of Infancy

Melanotic neuroectodermal tumour originates from neural crest cells and it is a osteolytic-pigmented neoplasm which primarily affects the jaws of newborn infants [45]. Microscopically, it is characterized by a biphasic population of pigmented and non-pigmented cells in a dense fibrous connective tissue stroma [11]. The tumour is recognized by the presence of epithelial-like cells that are arranged in small islands, which outline acinar or glandular structures. These cells are often large in size, with abundant cytoplasm which is rich in melanotic pigments. The second group of cells is generally grouped, but they are not very cohesive, which may be seen as islands or which are occasionally arranged in bunches, and are surrounded by pigmented epithelial cells [46]. Molecular studies suggested that large cells with melanin resembled a neuroepithelium, while small non pigmented cells resembled immature neuroblasts or differentiating neuroblasts. All the cellular types clearly have ultra structural features which are specific for the neurogenic cells [47,48]. Immunohistochemical studies suggested HMB 45 positivity in cuboidal cells [49,50]. Based on these studies, it has been suggested that Melanotic neuroectodermal tumour is derived from the epithelial nest that evolved at the time of the embryonic fusion during the facial process and this supports the Combination Theory explanation for the biphasic nature of this tumour.

Histologically Mimicking Biphasic Tumours

Myofibroblastoma

Myofibroblastoma is a benign stromal tumour of mesenchymal origin with a myofibroblastic differentiation. It is most often seen in the mammary stroma [51]. However, extramammary myofibroblastomas are reported among head and neck tumours [52]. It is considered to be rare in the oral and maxillofacial region, and so far, only three cases of oral myofibroblastomas have been documented [53-55]. Microscopically, the tumour tissue is characterized by spindle-shaped cells which are slender and are closely packed in short, straight, haphazardly intersecting fascicles, with hyalinized stroma. This tumour shows a wide spectrum of morphological appearances and thus, it is categorized into eight histological variants. These include – cellular, infiltrating, epithelioid, deciduoid -like, lipomatous, fibrous, myxoid and mixed variants. The intra lesional variability is caused by the fibro-myofibroblastic differentiation. Microscopically, epitheloid myofibroblastoma is characterized by epithelioid cells predominantly. These epithelioid cells are usually arranged in clusters or in an alveolar, solid or trabecular growth patterns and they are variably embedded in a myxoid to fibrous stroma. The epitheloid and stromal components of this tumour mimic a biphasic appearance [12,13]. The fact is that the broad morphological spectrum that the lesion predisposes to, is a potential diagnostic pitfall and that the microscopic appearance of this tumour can be mistaken for that of a biphasic tumour.

Neurilemmoma

Neurilemmoma is a benign neural neoplasm that originates from Schwann cells. Microscopically, the tumour is characterized by the presence of two patterns which are called Antoni A and Antoni B [56]. The Antoni A pattern is demonstrated by streaming fascicles of spindle shaped cells. These cells are often arranged in a pallisading manner around central acellular eosinophillic areas which are called Verocay Bodies. In contrast, the Antoni B pattern is demonstrated by less cellular areas and it is less organized. The spindle cells are haphazardly arranged within a loose myxomatous stroma [57]. It

has been suggested that the histological appearances of cellular Antoni A and paucicellular Antoni B areas are considered to be of a biphasic pattern [14], but they are not considered to be those of a true biphasic originated tumour.

Future Directions

Although histogenetic concepts have been proposed for the biphasic tumours, further explanation is needed for the exact mechanism of the biphasic drive in the tumour. The term, 'biphasic' represents the origin which is from two different components. The two cellular components may originate from the combination of ectodermal and mesenchymal derived tissues or within ectodermal or mesenchymal elements. The term, 'biphasic' relates to number of origin and not the stemness of the components. The term, 'bimorphic' is not a synonym. Bimorphic refers to two morphological structures rather than two different origins of the tissue. Melanotic Neuroectodermal Tumour of Infancy is characterized by two cellular components which originate from neurogenic cells and are displayed in two cellular structures and is thus bimorphic instead of biphasic. Changing the terminologies actually may not highlight diagnostic standards, but it may alter the therapeutic issues. Revisiting the terminologies in these tumours as to which are biphasic and bimorphic is anticipated, and this will eventually help in defining and categorizing biphasic tumours of jaws.

CONCLUSION

The histogenetic concepts of biphasic tumours explain the genesis of two cellular components which are involved in the process of tumourigenesis. Molecular studies are helpful in identifying the origin of bipasic tumours and they support their categorization . Histological interpretations of biphasic tumours are easy, due to the patterns of the cellular components. We may not prove anything by proposing new terminologies to the pre-existing literature, but their value adds to the therapeutics and prognosis of the tumour. As in the cases of carcinosarcomatous lesions, the biphasic nature of tumour identifies its aggressiveness and this can help in deciding the therapeutic strategy for it.

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