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Review Article

Nuclear Morphology in Oral Lesions- Memoir of an Anarchial Nucleus

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ABSTRACT

Every differentiated cell has a unique morphology with a characteristic nucleus. The function of the nucleus is to dictate the metabolic activity of the cell by transcription and translation. Any change endured by the cell necessitates the nucleus to instruct modifications in intracellular molecular pathwaysto adapt to the environment. Molecular changes within a cell bring about acclimatization of the cytoplasmic organelles and the nucleus, which can be visualized microscopically. This article describes the most frequently observed morphologies adopted by the nucleus in various pathologies.

Key words: Nuclear Morphology, oral Lesions, stains.

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INTRODUCTION

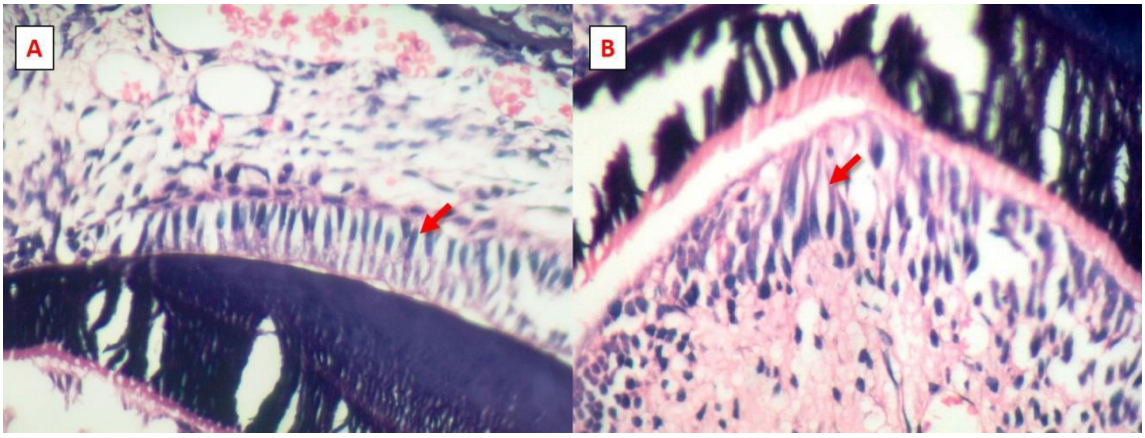
The nucleus forms the core organelle of the cell dictating the metabolic activity and functions performed by it. One of the rituals in diagnosingthenature of a biopsy tissue is based on the geometry and staining characteristic of the nuclei. Studies have been done extensively evaluating the nuclear morphology, staining characteristics and genetic alterations observed in tissues ofdiseases to determine the nature, particularly, ofneoplastic tissues. This article details the microscopic appearance of the nucleus in normal tissues and its appearance in different pathological conditions.

NUCLEI OF NORMAL TISSUE

One of the simple methods to scrutinize the nucleus is byanalyzing the staining characteristic and its relative shape, size and position within the cytoplasm and with respect to other cytoplasmic organelles.The size and shapeof the nucleus conforms to the morphology or outline of the cell. Columnar or cuboidal basal cells of the oral mucosa exhibit a round to ovoid nucleus while in other cells such as the mucous acini show flattened nuclei due to cytoplasmic mucin vacuoles. [1]To cite another example would be the "shape shifter" fibroblast of the connective tissuewhich generates anucleus based onits dichotomous nature. In its active phase, the nucleus is large and ovoid, pale staining while in the quiescent stage the nucleus is smaller, darker and elongated conforming to the spindled morphology.A similar elongated nuclear adaptation is observed with the elongated myoepithelial cells (cross section) located between basement membrane and secretory acinar cells of the salivary gland and also in the apocrine sweat glands of the skin.[2]

Generally, the nucleus in a normal cell maintains a position relatively in the center of the cell while the other organelles are distributed throughout the cytoplasm. The nuclei of certain specialized cells station eccentrically or position away from basement membrane to facilitate the function as can be seen in the mucous aciniof salivary gland, in odontogenic cells such as Ameloblasts and Odontoblasts (Figure-1) in the bell stage of tooth development.[3]

Figure – 1: Ameloblasts(A) and Odontoblasts (B) with nucleus away from secretory end of cell in Bell stage of development of tooth.



The staining characteristic of the nucleus depend on the executive activity or function performed by the cell. In highly active cells, such as the basal layers of the epidermis, oral mucosa and pilar cells, the nuclei tend to show higher degree of hematoxylin staining due to higher metabolic activity of these cells. Nuclei of superficial senile cells of the oral mucosa render a deep darker staining due to degeneration of the nucleus, known as pyknosis. The nucleus can also give a reduced or pale staining appearance with coarse or granular appearance which is described as vesicular or open nuclei, a feature seen in malignant tumors. Thus, in every hematoxylin and eosin stained slide, the hemotoxylin should stain the nuclear chromatin blue to bluish purple (depending on the chromatin content and organization) and be very distinct with the nucleoli appearing reddish purple.[4]

CELLULAR ADAPTATION

Cellular adaptation refers to the response of a cell to an external agent or environment and is proportional on the stimuli or agent, threshold of tolerable workload and the type of cell involved. Themajor types of cellular adaptation include atrophy, hypertrophy, hyperplasia, metaplasia and dysplasia. Atrophy is the decrease in the cell size resulting in overall reduction in the organ. It is often associated with various pathological conditions such as ischaemia, malnutrition. Hypertrophy and hyperplasia are two different adaptations that usually occur concurrently and clinically seen asa generalized increase in size of the affected tissue or organ.In hypertrophy,the increase in organ size is caused due toincrease in size of the individual cells while in hyperplasia the overall increase in organ size is attributed to the increase in number of the cells. Hyperplasia tend to occur in tissues comprising of cells capable of division while hypertrophy is adopted by highly differentiated tissue that show reduced proliferative activity such as the nervous tissue.[5,6] The morphological changes seen in the nucleus in dysplasia has beendiscussedin neoplasms.

Microscopically, the nuclear morphology of an atrophied cell varies based on the affected tissue. Diabetes mellitus is a disease that causes atrophy of the oral epithelium attributed to the decrease in rate of cell proliferation. Apart from the typical cytological changes mentioned above, the nuclei of the basal cells of the oral epithelium appear enlargeddue to compensatory loss of intracellular content.[7]While in atrophied muscles, the nuclei appear to be lost by apoptosis but no evidence of DNA breakage is observed.[8]

Hypertrophy affects muscle tissue more than any other tissue compared,in particular to the cardiac muscle. Nuclear crenation is the hallmark feature observed in cardiac muscle and forms the basis of scoring hypertrophy.[9]

NEOPLASM

Biopsy specimens received by the pathologist is thoroughly analyzed to rule out or consider a tumor by examining the cells for the cardinal features of dysplasia exhibited by a neoplastic lesion. The appearance of the nucleus, that is, the shape, size, staining intensity and the nucleoli is one among the dysplastic features to be analysed. Malignant tumors, particularly those arising from connective tissue demonstrate afurther feature appearing microscopically as granular or vesicular nuclei.

Differentiation and anaplasia are very closely related terms depicting the nature of the tumor. Differentiation is the degree to which a neoplastic cell represents the parent cell both morphologically and functionally. The well differentiated the tumor cell the more it resembles the normal parent tissue which can be appreciated with adjacent normal tissue of the biopsy specimen.

Anaplasia is the lack of differentiation and is considered the hallmark of malignant tumors. These features can be recognized in individual cells of malignant tumors which are represented by abnormal and bizarre nuclear morphology and by absence of any architectural similarity of the parenchyma to the parent tissue. The aggressiveness of a malignant tumor can be discerned microscopically by the presence of disproportional nuclear size, hyperchromatic nuclei, in most cases, the chromatin clumping (vesicular) seen in a pale staining nucleus. The nucleoli within the nucleus become large and prominent in malignancy (Figure - 2).

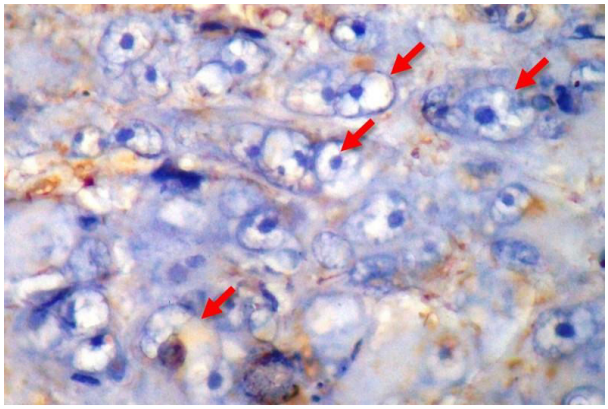


Figure 2 – Nucleus in Oral Squamous Cell Carcinoma exhibiting dysplastic features in IHC stained negative for Vimentin.

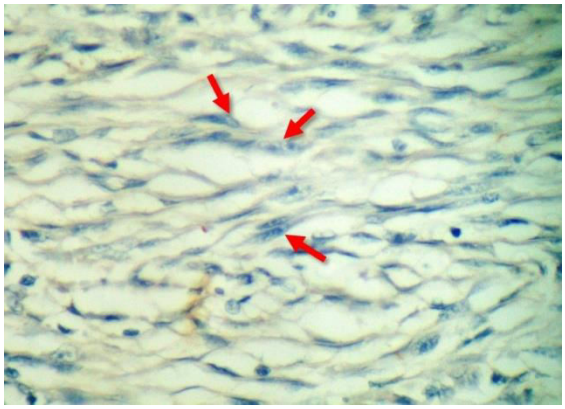


Figure – 3 – Nucleus in Leiomyosarcoma exhibiting dysplastic features.

The presence of mitosis illustrates the proliferative activity of the tumor cell and can be demonstrated even in benign tumors. Atypical mitosis, on the other hand, is morphological feature seen within the nucleus of undifferentiated tumors confirming the aggressive nature of malignancy.

Besides the dysplastic features identified within a neoplastic tissue, certain tumors show unique and pathognomonic appearances such as Leiomyomas and Ameloblastomas.

NUCLEI IN CERTAIN TUMORS SHOWING UNIQUE NUCLEAR CHARACTERISTICS

Fibrosarcoma is the malignant tumor of fibrous tissue simulating microscopically the spindled morphology of the fibroblast. The ultrastructure of the malignant cells corresponds to the microscopic feature. The nuclei of these tumors also show indentation of the nuclei with infrequent nucleoli.[10]

Leiomyomas are benign tumors of the smooth muscle origin histologically showing interlacing bundles of smooth muscle fibres. The peculiarity of these tumors is the appearance of the nuclei which are spindle shaped (conforming to the shape of the cell), with blunt ends, cigar shaped which is one of distinguishing feature with other nuclei of fibromatous origin where the nuclei is tapered. Even in the benign nature the nuclei of these tumors are quite vesicular. The histology of leiomyosarcoma demonstrate increased cellularity, nuclear and cellular pleomorphism and other typical features of malignancy, necrosis and hemorrhage. In addition to these features, an increased mitotic activity is observed denoting an invasive growth pattern (Figure - 3).[11]

Tumors of neural origin exhibit a histology composed of proliferating of spindle cells with a unique nuclear morphology. The nuclei are thin, delicate, dark and elongated;wavy which can be intermingled with neuritis seen in neurofibromas (Figure 4).

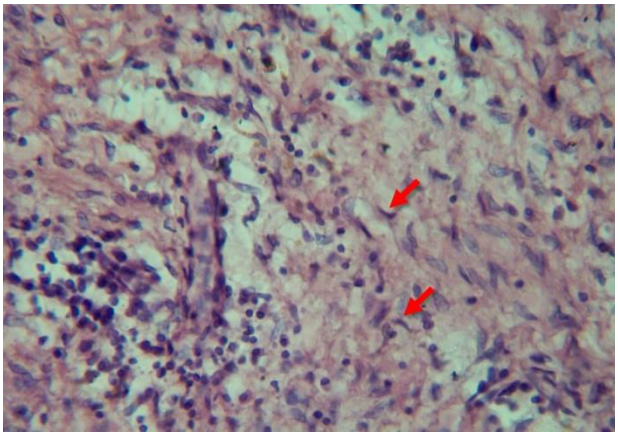


Figure – 4 – Nuclei seen in Neurofibroma

Histologically, Lymphomas are distinguished as Hodgkin's and Non Hodgkin's lymphoma by the presence or absence of the pathognomonic cell, the multinucleated Reed Sternberg cell. The mononuclear and the multinucleate Reed Sternberg cells are easily recognized by their large nucleoli. The ultrastructural features are common in both cell types. The nuclei are large, rounded at times oval with uniformly dispersed chromatin. The nucleoli are very large occupying a central position within the nucleus. Reed Sternberg cells consist of large multinucleated or bilobed nucleus with prominent nucleoli giving the characteristic "owl eye" appearance.T cell lymphomas usually possess large nucleus with dispersed chromatin and are, at times, hyperlobulated.[12]

Plasmacytoma comprise of round to ovoid cells with an eccentric nucleus showing the characteristic "cartwheel" appearance.

One of the odontogenic tumors which histologically show a unique cytology is the Ameloblastoma. The tumor cell show island or nest with tumor cell located peripherally with the nucleus situated away from the basement membrane simulating the ameloblast, the cell responsible for the production of hard tissue of the tooth.

MULTINUCLEATED GIANT CELL AND MULTILOBED NUCLEI

As with every cell, the size and the number of organelles in a cell depends on the function, differentiation and age of the cell including the nucleus. Cells performing more activity require an increased metabolic activity and cellular organelles as can be seen in blasts cells, cells responsible for development (Ameloblasts) and certain differentiated cells such as the osteoclasts.

Multinucleate cells are cells which comprise of more than one nucleus within the cytoplasm formed either by fusion of similar cells or by division of the nucleus. Osteoclasts were initially considered to form by union or fusion of osteoblasts a process known as syncytia. It was later proved that these cells develop by fusion of macrophages, thus, the monocyte phagocyte lineage being the precursor cells. Multinucleate cells or giant cells can be physiological or pathological. A few examples of physiological giant cells are osteoclasts seen in bones, trophoblasts in placenta, serous acinar cells of the salivary gland and skeletal muscle fibres. Multinucleate giant cells are seen in numerous pathological conditions like Langhans'sgaint cells seen in granulomatous lesions and tumor giant cells in many epithelial and mesenchymal conditions. In granulomatous lesions, these multinucleated giant cells are actively involved in destruction.[13]

The common feature to these giant cells is the presence of more than one nucleus and the differentiating features would be the number, position and appearance of the nuclei. The physiological giant cell, the Osteoclast contain fewer nuclei and appear morphologically similar to foreign body giant cells located in close approximation or within Howship's lacunae on the bone surfaces. While the nuclei of tumor giant cellsare numerous, usually containing more than 30 nuclei, are pleomorphic showing abnormal mitosis, seen in Giant cell tumor of bone, Osteosarcomas, Chondrosarcomas, Brown tumor of Hyperparathyroidism. Cherubism is a fibroosseous lesion occurring in children which also show the presence of giant cells which are found to be osteoclast like (Figure 5).[14]

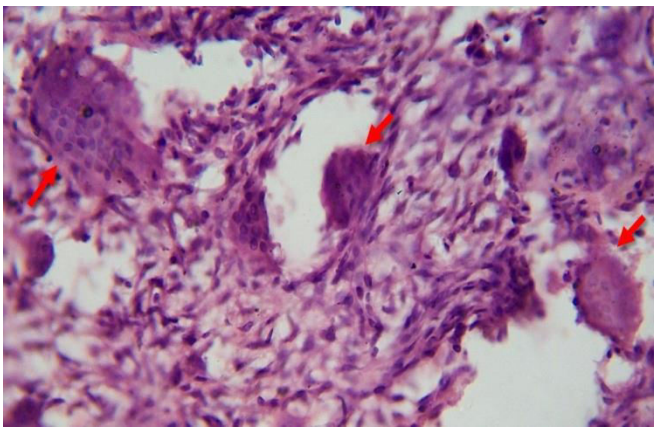


Figure – 5 – Presence of multiple nuclei observed osteoclasts in Cherubism.

Granulomatous disease such as Tuberculosis, Leprosy, Sarcoidosis exhibit giant cells within the granulomas. These giant cells are unique as the nuclei arrangement are restricted to a particular granuloma. Langhan's giant cells show a distinctive horse shoe shaped arrangement of the nuclei within the cytoplasm. Warthin-Finkeldey giant cells seen in Measles, HIV infection show the characteristic morphology of high nuclear to cytoplasmic ratio, irregular nuclei and crowded, sometimes even overlapping nuclei.[15]

Multilobed nuclei are those cells which exhibit nuclei with more than one lobe and are associated with the nuclear shape. Various diseases tend to show an alteration in shape, including ageing. Nuclei in certain physiological cells such the neutrophils and eosinophils show lobulation or altered nuclear shape for important cell functions. These alterations reduce the rigidity of the cells enabling them to pass or migrate through tight spaces of vessel linings as in inflammation. Studies have shown the three to four lobes of the neutrophils are joined by thin DNA filaments. The hypolobulations are associated with proteins of the nuclear lamina.

CONCLUSION

The morphology of the nucleus is as intriguing as the morphology of the cell. Knowledge of the dimensional characteristic of the nucleus in normal tissue and diseased tissuecan serve in not only the diagnostic process but also prompt further investigation to comprehend the etiopathogenesis of the disease.

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