***Review Article***

**Binucleated Cells: A Comprehensive Review of Locations, Mechanisms, Clinical Significance, and Diagnostic Applications**

**ABSTRACT**

**Background**: Binucleated cells are a type of cell that contains two nuclei within their cytoplasm and are commonly observed in both normal and pathological conditions. They play essential roles in physiological processes, such as tissue repair and adaptation, and are also implicated in various diseases. Understanding their formation and behavior is critical to uncovering their significance in health and disease. **Objectives**: This review aims to discuss the literature on binucleated cells, focusing on their presence in normal tissues and disease states, the mechanisms of their formation, their clinical significance, and potential implications in diagnostics and therapeutics. **Methods**: For this narrative review, PubMed, Medline, and Google Scholar were utilized to search for articles about binucleated cells. The final set includes 23 academic articles that matched the inclusion criteria. **Results**: The reviewed studies indicate that binucleated cells are present in various normal tissues, including the liver, bone, and spleen, where they contribute to regeneration and immune response. They also play significant roles in autoimmune diseases, infections (e.g., HPV and HSV), and cancers, serving as crucial diagnostic markers for early detection and disease progression. Conclusions: Binucleated cells represent a valuable tool for understanding and addressing diseases. Their biological and pathological roles open new avenues for scientific advancements in diagnostics and treatment strategies.

**Keywords**: Binucleated cells, Cell fusion, Cytokinesis failure, Polyploidization, Endoreplication, Binucleated cells in infection.

**1. INTRODUCTION**

Binucleated cells are characterized by the presence of two distinct nuclei within a single cell **[1].** They are observed not only in malignant tumors but also in normal tissues **[2].** In normal tissues, they can be found in the heart, muscle cells, platelet progenitor megakaryocytes, liver parenchyma, and bladder **[3].** In malignant tumors, they appear in malignant epithelium tumors, pancreatic cancer, angiosarcoma, and acute myeloid leukemia **[4].** The biological importance of binucleated cells in normal tissue lies in their ability to protect tissues from genetic damage or serve as part of normal development, as seen in liver and heart tissues, where they help prevent cellular degeneration **[5].** In tumors, binucleated cells may indicate genetic instability, contributing to tumorigenesis and metastasis. Their presence can be associated with specific stages of tumor development **[6],** and may also act as a marker for genetic damage in cancer cells, which facilitates the transformation of normal cells into cancerous ones **[7].** There are two different mechanisms for the formation of binucleated cells: cell-cell fusion and abnormal mitosis **[8].** Cell fusion is a specialized biological process in which cell membranes merge to create a new cell containing two or more nuclei. This process is crucial in many biological systems **[9].** Abnormal mitosis refers to a cell division process where errors occur, such as cytokinesis failure **[10],** chromosomal instability, and cellular stress **[11].** Binucleated cells may be reversible or irreversible. Reversible binucleated cells can divide and proliferate **[12],** whereas irreversible binucleated cells usually undergo cell death or senescence due to significant genetic mutations, preventing them from proliferating or surviving for long periods **[13].** While binucleated cells have been linked to certain diseases, their role and underlying mechanisms are not fully understood. There is a need to investigate the biological significance of binucleation and its association with pathological states. This narrative review aims to bridge this gap by summarizing recent findings, highlighting their clinical relevance, and providing a foundation for future research in the field.

**2. MATERIALS AND METHODS**

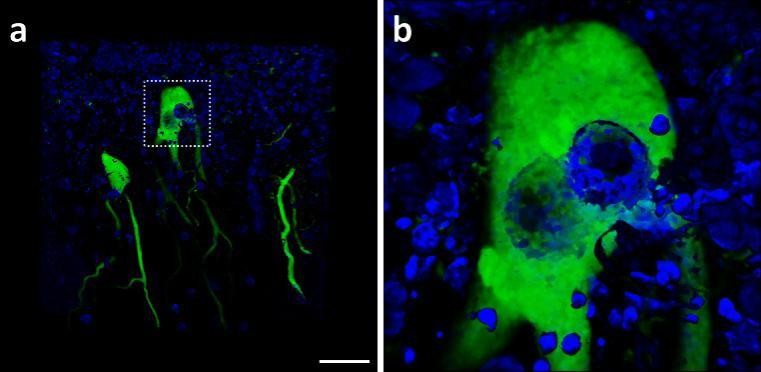
In this review, I conducted a narrative analysis and discussed the relevant literature that has studied binucleated cells with various designs. The literature was searched on PubMed, Medline, and Google Scholar using the Chrome browser. The search terms were "binucleated cells", "mechanism of binucleation", "cell fusion", "cytokinesis failure", "binucleated cells in infection", and "polyploidization". The inclusion criteria were the English language, articles addressing research published within the last 10 years. The exclusion criteria included non-English language, articles not addressing the research topic, studies that do not directly focus on binucleated cells, duplicated studies, articles lacking full-text availability, and research published more than 10 years ago. I finally selected a total of 23 studies. Besides these selected studies, several other studies were chosen from their references. The review aimed to answer the following questions: What are binucleated cells, and how are they formed? What is the role and reasons for binucleated cells in tissue and cytological smears? How are they associated with infections and cancers? And how can binucleated cells be used as diagnostic markers in modern medicine?

**2.1. Binucleated cells in normal tissues**

**2.1.1 In bone marrow**

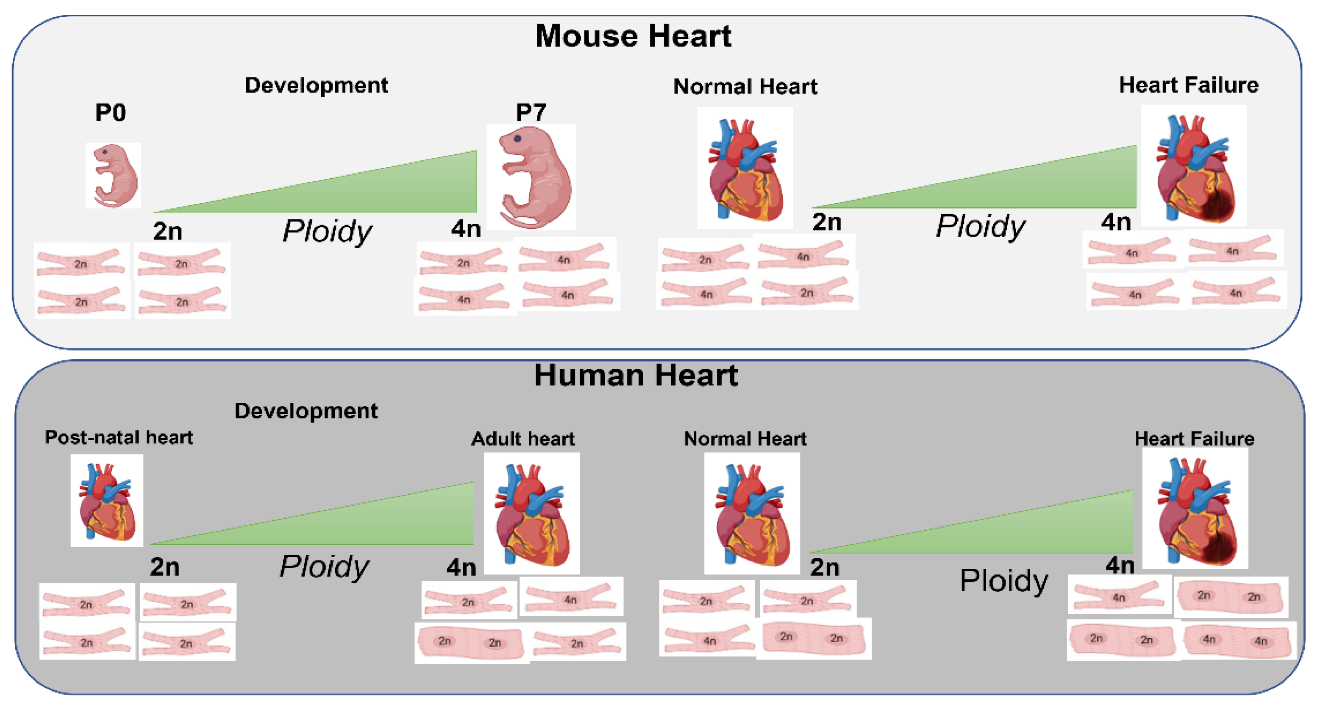
Recent research challenges the belief that adult cells are restricted to their tissue of origin, highlighting their plasticity and potential to differentiate into unrelated lineages, termed adult cell plasticity **[14].** This concept emerged from bone marrow transplantation studies, showing that bone marrow-derived cells (BMDCs) could transdifferentiate into neuronal-like cells **[15].** Bone marrow contains two key stem cell types: hematopoietic stem cells (HSCs), which produce blood cells, and mesenchymal stromal cells (MSCs), which differentiate into mesodermal lineages like osteocytes and adipocytes **[16].** Both BMDCs and MSCs have shown the ability to transdifferentiate into neural-like cells in vitro **[17]** and in vivo **[15].** However, some studies debate these findings, suggesting neural-like morphologies in vitro may result from cytoplasmic retraction rather than neurite extension **[18].** Additionally, BMDCs might fuse with host neurons rather than undergoing transdifferentiation, explaining the presence of binucleated neurons after BMDC transplantation **[19].** Bueno et al. **[20]** demonstrated in an experimental study that human BM-MSCs can form binucleated cells, suggesting these cells play a role in neural differentiation without fusing with existing neurons. These findings underscore the potential of neuronal transdifferentiation and its implications for neurodegenerative disease therapies **[21].**

**2.1.2. In the brain**

****Kemp et al. **[22]** explored the occurrence of binucleated cells in the brain, particularly in cerebellar Purkinje cells, arising from bone marrow cell fusion. This process is believed to occur in response to injury or inflammation and may represent a novel mechanism for neuronal repair. Research indicates that cell fusion events increase under conditions such as aging, radiation exposure, inflammation, and chemotherapy **[23].** The role of immune cell infiltration in forming binucleated cells remains unclear, although soluble factors may significantly influence this process **[23].** Binucleated cells are hypothesized to aid in neuroprotection and the restoration of homeostasis in neurodegenerative diseases, making them a promising area for therapeutic research. These findings provide insights into endogenous neuronal repair mechanisms, potentially offering new avenues for treating neurodegeneration and brain injuries **[23].**

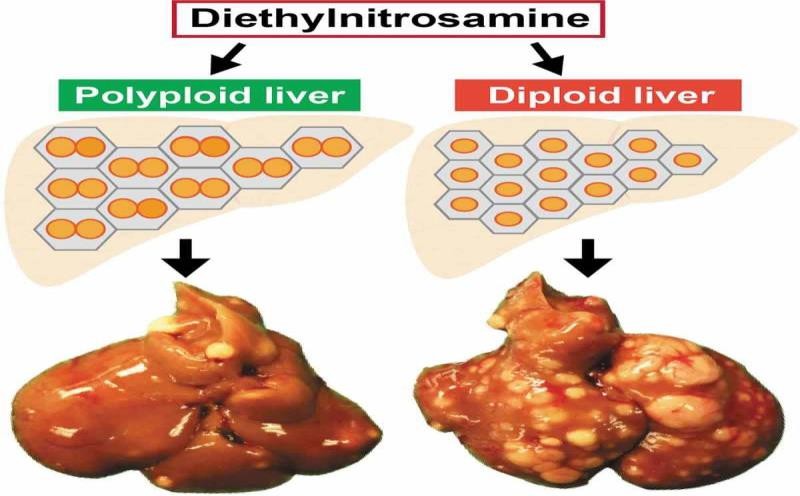
**Fig.1.** A binucleated Purkinje cell in the human cerebellum. This 3D confocal image shows cells in the human cerebellum, with Purkinje cells labeled using the Calbindin-D28K marker (green) and DAPI nuclear stain (blue). The hatched region in part (A) corresponds to the magnified image shown in part (B), with a scale bar of 25 μm **[22].**

**2.1.3. In the heart**

Binucleated cardiomyocytes (CMs) are polyploid heart muscle cells, often resulting from cytokinesis failure during cell division, where cytoplasmic division does not follow nuclear division **[24].** These cells are particularly significant due to their enhanced contractile function, larger cellular size, and distinct electrical properties, which are crucial for maintaining coordinated heart rhythms **[25].** Binucleated CMs are more prevalent in the ventricles, supporting their specialized structural and functional roles **[26].** The formation of binucleated and polyploid CMs occurs through regulated failures in karyokinesis and cytokinesis, distinct from the uncontrolled mitotic failures seen in cancer cells. This programmed process reduces the proliferative potential of polyploid CMs, limiting their ability to regenerate after injury **[27].** Despite questions about transcriptional differences between diploid and polyploid cardiomyocytes, current findings suggest that transcriptional profiles may be more injury-dependent than nucleation-related, necessitating further research **[27].** Developing cardiomyocytes possess a greater regenerative capacity due to their ability to divide during the embryonic stage. In contrast, most adult cardiomyocytes lose this capacity postnatally, becoming "acytokinetic," which limits heart regeneration after injury **[28].** The rise in multinucleated and polyploid CMs is linked to a diminished capacity for regeneration, as these cells cannot effectively replace dead cells **[29].** Metabolic reprogramming has been identified as a potential mechanism to enhance the regenerative capacity of the heart. This process increases cell cycle activity in mononuclear diploid CMs, potentially improving cardiac repair post-injury. Activation of developmental signaling pathways in the heart can further promote this reprogramming and enhance recovery **[28].** This highlights the role of binucleated cardiomyocytes in heart function, their contribution to cardiac efficiency, and the challenges they pose in regeneration and repair.

**Fig.2. The relationship between cardiomyocyte polyploidy, development, and heart injury [28].**

**2.1.4. In Liver**

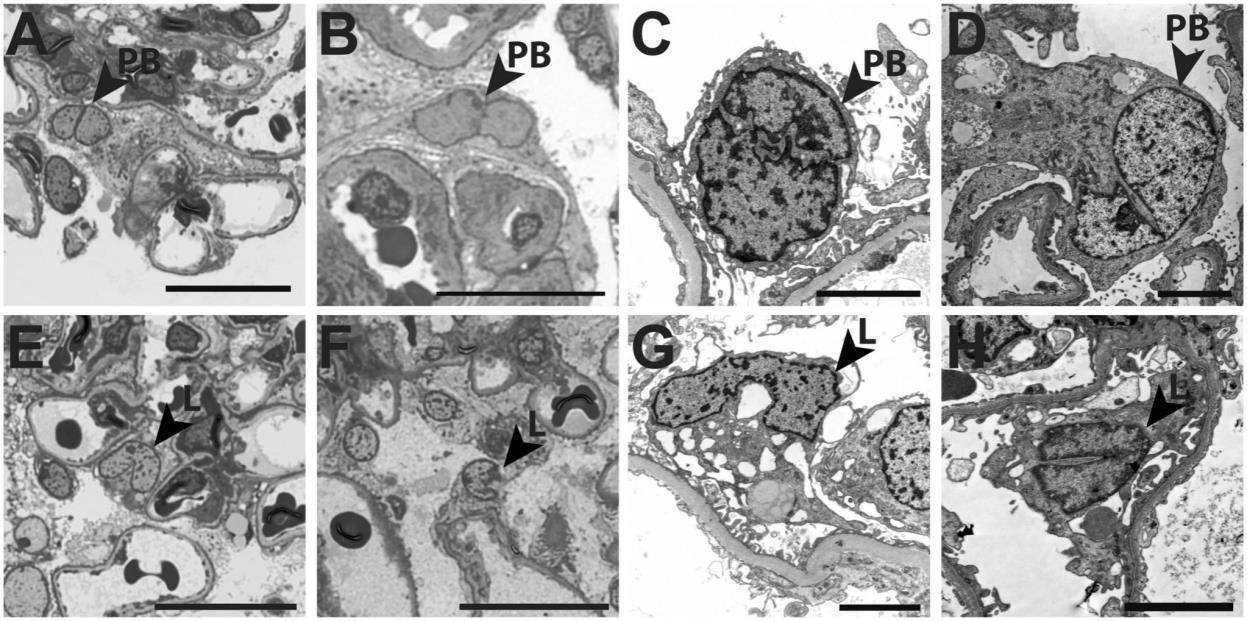
****The liver is an organ that carries out essential functions such as nutrient synthesis and distribution, storage of amino acids, lipids, and carbohydrates **[30],** These functions are conducted primarily by hepatocytes. At birth, every hepatocyte contains a single nucleus with a 2n DNA content, making them diploid. As development progresses after birth, hepatocytes typically become polyploid due to the failure of cytokinesis **[31].** Polyploid hepatocytes can take many forms: they can be tetraploid (binucleated with two 2n nuclei or mononucleated with one 4n nucleus) or octaploid (binucleated with two 4n nuclei or mononucleated with one 8n nucleus), and the proportion of polyploid hepatocytes rises with age **[32].** The mechanisms that can lead to polyploidization in hepatocytes are: cell fusion and alternative cell cycling **[33].** Zhang et al **[34]** conducted a review article on the origins and functions of hepatic polyploidy and hypothesized that polyploidy in the liver is regulated during development and in response to cellular stress or disease. It is hypothesized that polyploidy enhances the metabolic capacity of hepatocytes to support rapid growth **[35].**

**Fig.3. Polyploid hepatocytes safeguard the liver against tumorigenesis induced by mutagens [34].**

**2.1.5. In the lung**

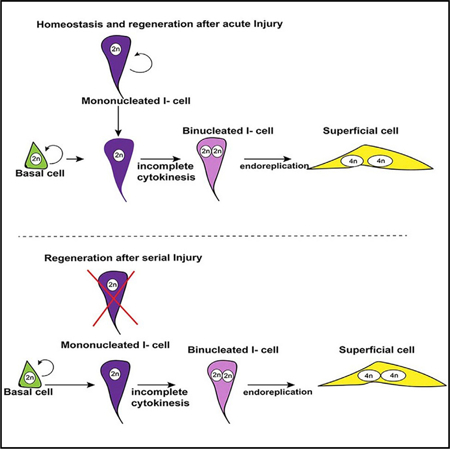
Guild et al **[35]** conducted an experimental study on evidence for lung barrier regeneration by differentiation before binucleated and stem cell division, focused on understanding the mechanisms of lung tissue repair after injury, specifically in the alveolar epithelial layer, the study explores how cells regenerate, particularly the role of stem cells (AT2) and binucleated cells in tissue repair. The lung epithelium consists of a thin cellular layer that plays a dual role in gas exchange and preventing fluid leakage from capillaries into alveoli **[36].** Given these limitations, the alveolar epithelium has developed into a fragile, simple monolayer made up of cuboidal, surfactant-producing alveolar type II (AT2) cells and extremely thin alveolar type I (AT1) cells **[37].** When this epithelium layer is damaged, it is rapidly repaired without scarring through the action of ~~alveolar type II~~ (AT2) stem cells, which differentiate into ~~alveolar type I~~ (AT1) cells to restore functionality **[38].** Binucleated AT2 cells play a critical role in the repair process. When AT2 cells are depleted due to their transformation into AT1 cells, binucleated cells undergo a unique division process. First, they undergo ploidy reduction (reduction in DNA content), followed by further stages of cell division to replenish the depleted AT2 cells. This process is regulated by epidermal growth factor receptors (EGFR) and the surrounding cellular microenvironment, ensuring rapid and efficient repair to maintain alveolar function **[38].**

**2.1.6. In renal and urothelium**

Mühldorfer et al. **[39]** studied binucleation in podocytes, highlighting its association with foot process widening in renal diseases such as minimal change disease (MCD), IgA nephropathy (IgA-GN), lupus nephritis (LN), and diabetic nephropathy (DN). Podocytes are critical components of the glomerular filtration barrier **[40],** and they are terminally differentiated cells that typically do not proliferate. However, under conditions of renal injury or stress **[41],** podocytes may re-enter the cell cycle but fail to complete division **[42],** leading to the formation of binucleated or multinucleated cells **[43].** The study found binucleated podocytes prevalent in renal biopsies, particularly in IgA nephropathy. Their presence in IgA-GN patients showed a weak correlation with glomerular structural damage and serum creatinine levels. However, no significant association was observed between binucleated podocytes and kidney function in other renal diseases. Challenges in accurately classifying podocyte nuclei were noted due to morphological variations. The findings suggest that binucleated podocytes could serve as markers of renal damage, necessitating further research to determine their role in disease progression.

**Fig.4. Potential bi-nucleated and lobulated podocytes in renal disease. Representative examples from podocytes with potential bi-nucleated (A–D; arrowhead, PB) and lobulated podocytes (E–H; red arrowhead, L) were shown. Scale bar represents 20 µm in semi-thin sections (A, B, E, and F) and 4 µm in electron microscopic pictures (C, D, ,G and H). A color version of the figure is available in the online supplemental material [39].**

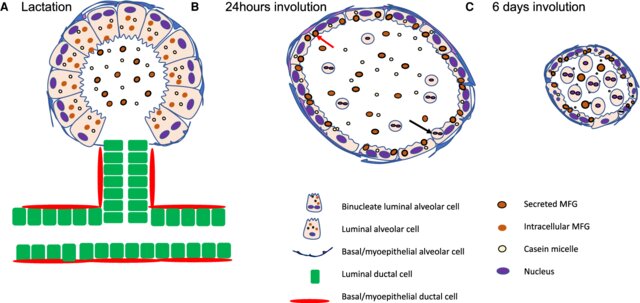
Wang et al **[44],** conducted an experimental technique on polyploid superficial cells that maintain the urothelial barrier. The urothelium serves as an epithelial barrier stretching from the renal pelvis to the bladder neck. It protects against pathogens and toxins while regulating the movement of water and ions between the mucosa and the underlying tissues. Polyploid cells in the urothelium are formed through incomplete cytokinesis, where cells enter mitosis but do not complete the division, resulting in binucleated cells. These cells can further increase their DNA content through endoreplication, which allows them to adapt to environmental changes **[45].** These polyploid cells contribute to the integrity and function of the urothelial barrier, which is essential for protecting the underlying tissues from urine and pathogens **[46].**



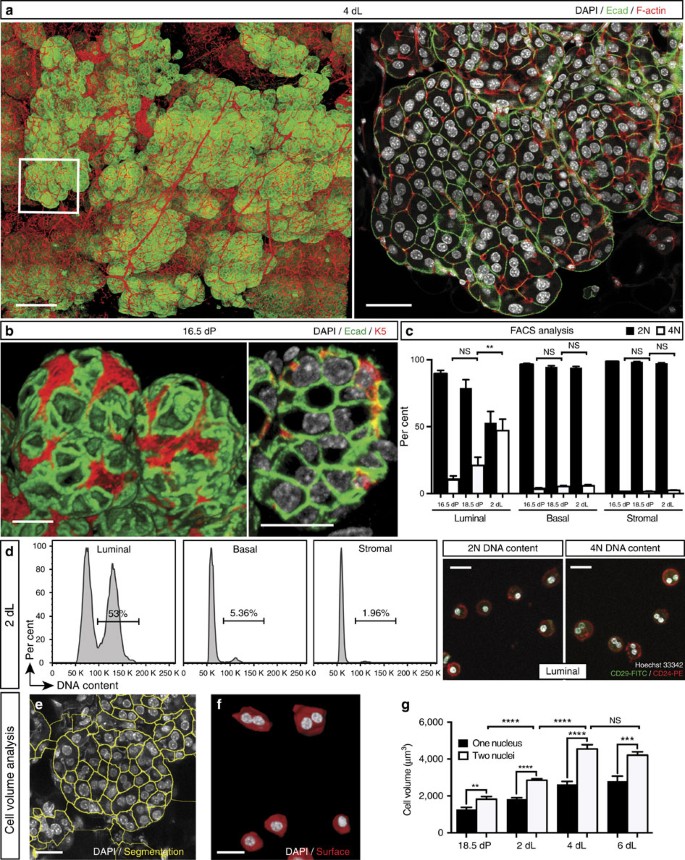
**Fig.5.** Homeostasis and regeneration after acute injury **[44].**

**2.1.7. In the mammary gland**

**[47]** explored the mammary epithelium, focusing on the role of binucleated alveolar epithelial cells during lactation. The mammary gland undergoes structural changes throughout life stages such as puberty, pregnancy, lactation, and involution **[48].** At birth, it features a rudimentary ductal structure composed of basal/myoepithelial cells expressing keratin 14 (K14) and luminal cells expressing keratin 8 (K8) or hormone receptors (ER+/PR+) **[49].** During lactation, binucleated cells play a pivotal role by producing large amounts of milk proteins, lipids, and carbohydrates to nourish offspring **[50].** These cells emerge as polyploid during lactation onset, increasing cytoplasmic volume to support organelles like ribosomes, ER, and Golgi apparatus, essential for milk synthesis **[51].** Their larger size also enhances apical surface area, facilitating efficient milk secretion. This highlights the adaptive significance of binucleated cells in lactogenesis **[52].**



**Fig.6. The structure and morphological changes in mammary gland during lactation and involution [53].**

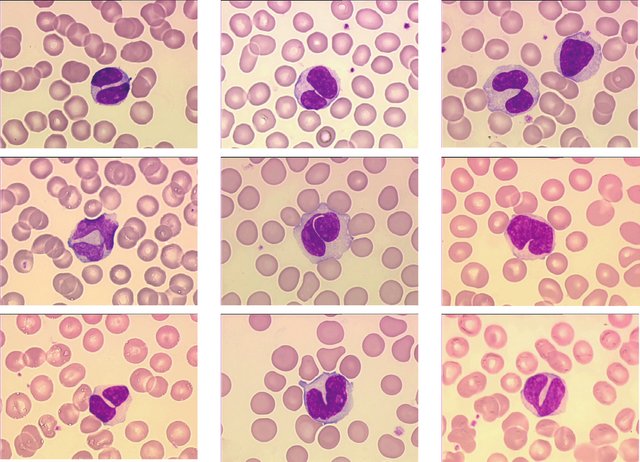


**Fig.7. Confocal image of a mammary ductal portion [47].**

**2.1.8. In oral mucosa**

Oliveira et al. **[54]** conducted a study on the use of psychotropic drugs among health science students, focusing on the prevalence of binucleated cells in the buccal mucosa. They found a high prevalence of psychoactive drug use, with a statistical association between drug use and the occurrence of binucleated cells in the oral mucosa. Although more common in females, this difference was not statistically significant. Other studies have shown that stress, anxiety, and depression, particularly in females, are linked to cellular changes, including binucleation **[55].** Similarly, Minhas et al. observed binucleated cells in both irradiated cancer cells and normal buccal mucosa of patients receiving chemoradiotherapy, indicating that ionizing radiation also induces binucleation.

**2.1.9. In the spleen**

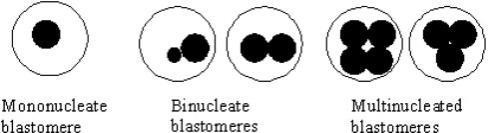
Sun et al. **[56]** investigated the role of binucleated cells in persistent polyclonal B-cell lymphocytosis (PPBL) and their importance in differentiating it from malignant lymphomas. Analyzing a spleen sample from a 38-year-old woman with progressive splenomegaly, the study found that binucleated cells are a hallmark of PPBL, frequently observed in peripheral blood **[57].** These cells result from abnormal B-cell division, likely triggered by chronic antigenic stimulation **[58].** Despite PPBL's resemblance to lymphoma in histological and immunophenotypic features, genetic and clinical analyses are essential for accurate differentiation, preventing unnecessary treatments **[58].**

**Fig. 8. Morphologic features showing typical binucleated cells in a PPBL patient [56].**

**Fig.9. Histological features of the spleen. Images of the HCE-stained spleen sections at 20x (A), 100x (B), and 400x (C, D) magnification showing expansion of the white pulp nodules and significant infiltration of the red pulp by small mature lymphocytes with minimal cytologic atypia. Occasional binucleated lymphocytes are noted in the splenic sinusoids, indicated by black arrows (C, D, and D inset) [56].**

**2.1.10. In emberyo**

Xanthopoulou et al **[59]** study the nature and origin of binucleate cells in human preimplantation embryos: relevance to placental mesenchymal dysplasia. The study focused on understanding the formation of binucleate cells (Binucleate Blastomeres) in human embryos during the early stages of preimplantation development, to investigate the origin and mechanism of these cells, taken biopsies from embryo making an analysis and suggested that binucleate cells form due to the inactivity of cell-cycle checkpoint genes during the early stages of embryo development **[60],** this leads to tetraploid mosaicism, which is associated with arrested embryos and poor development **[61].**

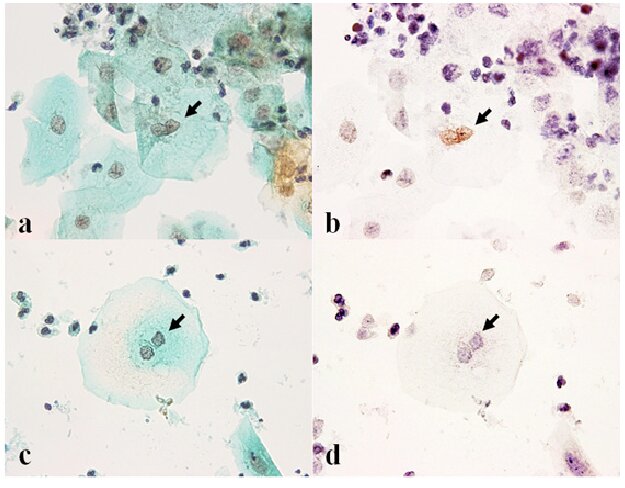
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**Fig. 10. Nuclear abnormalities seen in human preimplantation embryos [59].**

**2.2. Binucleated cells in infections**

**2.2.1. HPV Infections**

Binucleated cells serve as key markers in HPV-related infections. Okayama et al. **[62]** identified binucleated cells as the most prevalent cytological marker in anal Pap smears of HIV-positive patients, aiding in the early detection of anal intraepithelial neoplasia (AIN). Okodo et al. **[63]** and **[64]** differentiated between binucleation in high-risk HPV (hr-HPV) and candida infections, noting that binucleated cells with positive compression are predominantly linked to hr-HPV, whereas reactive cellular changes (RCC) in candida infections are inflammation-driven. Okayama et al. [65] confirmed the predictive value of binucleated cells in hr-HPV infections, supporting early identification of HPV-related cancers.



**Fig.11. Compression-Positive Binucleated Cells: (a) Pap staining (40×), (b) positive nuclear staining by in situ PCR with high-risk-HPV-specific primers (40×). Compression-negative binucleated cells: (c) Pap staining (40×), d) negative nuclear staining by in situ PCR with high-risk-HPV-specific primers (40×) [63].**

**2.2.2. Meningitis**

Delc et al. **[66]** analyzed cerebrospinal fluid (CSF) cytology in viral meningitis and meningoencephalitis, observing binucleated lymphocytes and plasma cells as markers of intense immune activation. These findings reflect the robust immune response to viral inflammation and assist in disease characterization.

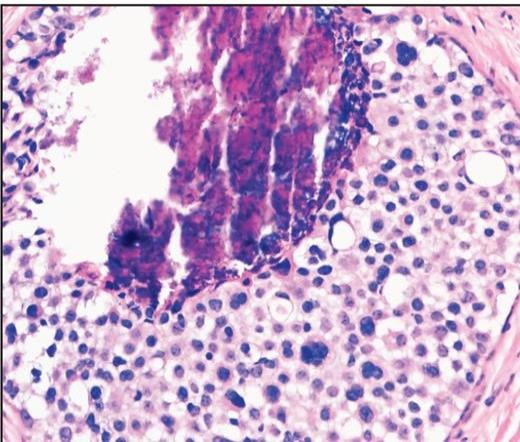
**2.2.3. HSV Infections**

Kannan et al. **[67]** described binucleated cells as a hallmark feature in HSV infections, especially in Papanicolaou-stained cervical smears. These cells exhibit nuclear molding, intranuclear inclusions, and a ground-glass appearance, serving as a crucial diagnostic marker for reducing misdiagnosis and unnecessary interventions **[68].**

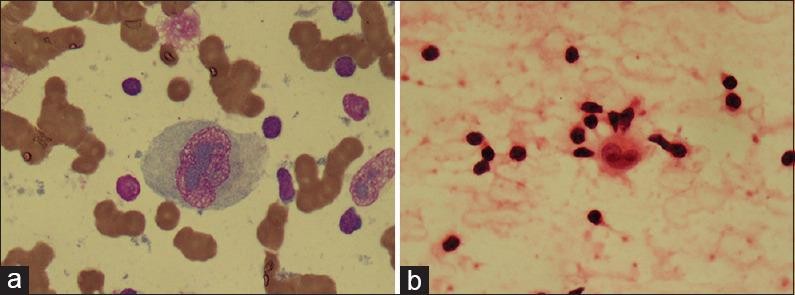
**2.2.4. Leishmaniasis**

Daneshbod et al. **[69]** highlighted binucleated cells in mucosal leishmaniasis (ML) cases, often observed alongside Leishman-Donovan bodies, the causative agents of the disease. This combination supports accurate cytological and histopathological diagnosis of ML.

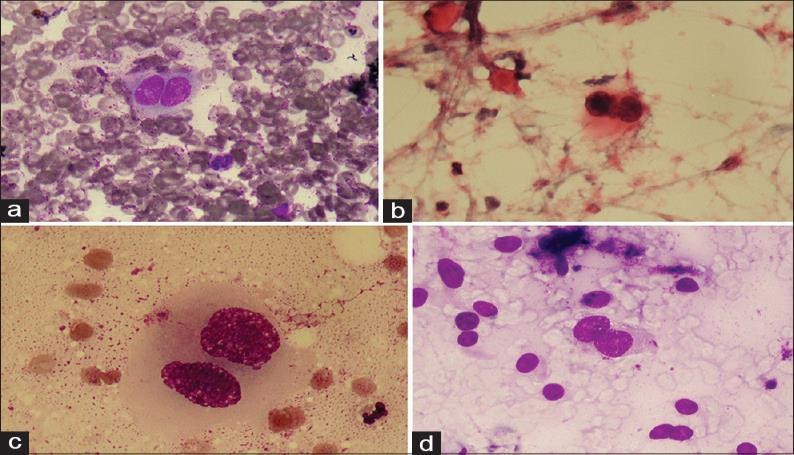
**2.3. Binucleated cells in cancer**

****Blanco et al **[70],** studied bi- and multinucleated cells as a histological marker that can be used to differentiate between various types of lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) in breast tissue. It focuses on comparing three types: Classic lobular carcinoma in situ (CLCIS), Pleomorphic lobular carcinoma in situ (PLCIS) and Ductal carcinoma in situ (DCIS). To enhancing the differential diagnosis between the subtypes of LCIS and DCIS and highlighting the presence of bi- and multinucleated cells as an objective marker to facilitate diagnosis. they finding that binucleated cells were more frequent in PLCIS (100% of cases) compared to CLCIS (54%) and DCIS (43%).

**Fig.12. Pleomorphic lobular carcinoma in situ demonstrating scattered binucleated and multinucleated cells [70].**

Priyadharshini et al **[71],** conducted a retrospective study on 2086 aspiration cytosmears/imprint smears, the slides were examined to identify the presence of binucleate Reed-Sternberg (RS) cells and RS-like cells, cases containing binucleate cells were classified into different categories according to their corresponding histopathological diagnoses, and their cytomorphological features were analyzed and compared. They revealed that the presence of RS-like cells was identified in 100% of HL cases, 30% of NHL cases, 12.9% of carcinoma cases, and 0.7% of benign/inflammatory cases. The analysis of cytomorphological features showed that certain characteristics, such as eosinophilic nucleoli, eosinophils, and cell clustering, could aid in distinguishing HL from other conditions. However, relying solely on cytomorphological features has limitations in differentiating true RS cells from RS-like cells, emphasizing the need for further ****histopathological examinations.

**Fig.13. (a) RS cell in Hodgkin's lymphoma showing pale-greyish magenta–colored inclusion-like nucleoli (MGG, ×100) (b) RS cell in Hodgkin's lymphoma showing eosinophilic inclusion-like nucleoli (H and E, ×100) [71].**

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**Fig.14. RS-like cell in other malignancies (a) non-Hodgkin's lynmphoma (MGG x100) (b) RS- like cell in non- Hodgkin's lymphoma (H and E, ×100) (c) RS-like cells in carcinoma (MGG, x100) (d) RS-like cell in sarcoma (MGG, ×40) [71].**

**2.4. Detection of binucleated cells**

Immunohistochemistry (IHC): Uses specific antibodies like P16 and P53 to highlight abnormal cell division via chromogen staining under a microscope **[72].** Cytochemical Staining: Methods such as Papanicolaou staining detect nuclear changes, including binucleation **[73].** Digital Cytometry: Employs digital imaging to identify and measure binucleated cells with high accuracy **[74].** Fluorescence Microscopy: Uses fluorescent dyes for sensitive detection of nuclei in cellular samples **[75].** These methods effectively identify binucleated cells and contribute to understanding cellular abnormalities.

**3. DISCUSSION**

**Binucleated cells have emerged as intriguing cellular entities with diverse implications in both physiological and pathological contexts. Their presence in normal tissues, including the liver, bone, spleen, and mammary gland, suggests that they may play active roles in tissue remodeling, regeneration, and maintenance of function. These cells are also frequently identified in disease settings, such as cancers, viral infections (e.g., HPV and HSV), autoimmune conditions (e.g., persistent polyclonal B-cell lymphocytosis), and even embryonic developmental disorders. Such wide distribution highlights their diagnostic, prognostic, and potentially therapeutic relevance. Despite their documented presence in various biological systems, a comprehensive understanding of binucleated cells remains limited. Most existing studies are descriptive or observational, relying on cytological smears, histopathological samples, and immunohistochemical staining. While these have contributed to mapping the occurrence of BNCs across different tissues, they often fall short in elucidating the underlying molecular mechanisms or functional consequences of binucleation. Multiple mechanisms have been proposed for the formation of binucleated cells, including incomplete cytokinesis, cell fusion, mitotic slippage, and DNA replication errors. In cancers, failure of mitotic checkpoints or disruption of the spindle assembly can lead to abnormal binucleation, potentially contributing to chromosomal instability and tumor progression. In contrast, in regenerative tissues such as the liver and kidneys, binucleated cells are often associated with tissue repair and recovery following damage or fibrosis. This dual behavior suggests that binucleation may serve as both a response to injury and a marker of dysregulation, depending on the context. However, the precise regulation of these processes remains unclear. The signaling pathways, gene expression profiles, and environmental triggers that determine whether binucleation leads to regeneration or malignancy have not yet been well-characterized. For example, while binucleation in hepatocytes is considered a normal adaptive mechanism, its role in hepatocellular carcinoma remains controversial. This ambiguity reflects a broader challenge in distinguishing physiological from pathological binucleation. Binucleated cells have demonstrated potential value as diagnostic biomarkers. In cytopathology, their detection can support early diagnosis of viral infections such as HPV or HSV, both of which are associated with cancer development. Moreover, in autoimmune conditions like PPBL, the persistent presence of BNCs may indicate chronic immune stimulation. Despite these associations, the interpretation of binucleated cells remains variable. Differences in staining techniques, sampling methods, and observer expertise can influence detection and classification. Therefore, there is a critical need to establish standardized diagnostic criteria and thresholds for the identification of BNCs across different diseases and tissue types.**

## **4. CONCLUSION**

Binucleated cells are not merely a biological phenomenon; they serve as a window into understanding health and disease. Their natural presence reflects their role in regeneration and cellular functions, while their association with diseases such as cancer and infections highlights their significance in diagnosis and treatment. Understanding the mechanisms behind their formation opens new horizons in regenerative medicine and disease targeting. They are not just pathological markers but also a promising scientific tool that can reshape how we approach diseases.

**CONSENT**

The patient’s written consent has been collected.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

As a result, the Author (s) declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

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