

Cell Block Technique In The Diagnosis Of Oral Lesions – A Methodical Assessment

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ABSTRACT

Aim: This review aims to explore the use of cell block cytology in the diagnosis of oral lesions

Background: Utilizing the science of cytopathology is cost effective, fast, simple and accurate. Over the years, with the improvements in technical aspects and the appearance of cell block technique in cytopathology, the gold standard of “must have tissue to make an accurate diagnosis” is rapidly changing.

Review results: The review identified articles on use of cell block technique in oral lesions. The current research studies on this technique for oral lesions are very sparse. Most of the identified studies were limited to odontogenic lesions.

Conclusion: Though the cell block technique is being practiced for more than a century now for non-oral lesions, its practice among head and neck lesions is not up to par. Being cost effective, fast, simple, accurate and requires only a small tissue sample, its utilizing in oral diseases needs to be explored further.

Key Words: Cytology, Cell Block, Cytodiagnosis, Odontogenic Keratocyst, Immunohistochemistry**INTRODUCTION**

The cell block technique is a histological technique, used for processing cytological specimens. It involves the collection of small tissue fragments from a fine needle aspiration specimen, which is then processed to form a paraffin block. It is gaining wide acceptability due to its ability to provide increased cellular yield and improved diagnostic accuracy.¹⁻³ It is known to provide better diagnostic accuracy by increasing the cellular yield and retaining good cytomorphic features.^{1,3-6} Another advantage is its unlimited storage and obtaining multiple sections for routine staining, special staining and immunocytological procedures.^{1,3,7-9}

The cell block technique is used often in medical pathology for fine-needle aspirations, gynecology samples, peritoneal fluid, bronchial washings, pleural fluid and other cytological specimens.^{1-3,6} It is one of the oldest method of processing cytological material, described by Mandlebaum in 1900 for studying exudates.¹⁰ The aspirated material is centrifuged, sedimented tissue obtained is processed, paraffin-embedded, cut, stained and microscopically analyzed.^{2,3,6} It retrieves even small tissue fragments from the cytological specimen and provides increased cellular yield and improves diagnostic accuracy.^{3,5,6} It can be used as an useful adjunct to cytospin in establishing a better and definitive diagnosis.¹¹⁻¹³ It bridges the gap between cytology and histology.^{4,5} However, it is rarely been used in dentistry. Couple of studies have shown positive use of cell block as an adjunctive technique in the possible diagnosis of cystic lesions of the jaw.^{1,2}

The advantage of this technique is, it is simple, reliable, fast, safe, cost-effective, requires no special training or instrument and is reproducible even in resource-limited rural areas.^{1,7,9} The decrease in cellular dispersion aids in obtaining maximum cellular concentration.^{2,9} The paraffin embedment aids in better analysis of the collected liquid content and in obtaining fine sections for microscopic analysis.¹ It produces less background staining, preserves morphologic features and tissue architecture, thus aiding in recognition of histological patterns of diseases.^{4,7} Another advantage is its unlimited storage and obtaining multiple sections for routine staining, special staining and immunocytological procedures.^{1,7}

A wide range of histologic fixatives have been used for cell blocks, primarily buffered formalin, Bouin solution, picric acid fixative, Carnoy fixative, and ethanol. Formalin, an acceptable tissue fixative, also has been used widely for cell blocks by most researchers, however it may not be suitable for cytology as it may not well preserve the nuclear and cytologic details.⁹ Initially when the technique was introduced, 10% alcohol-formalin was used for fixation. The proteins cross-link forming a gel by the action of formalin, thus preventing its dissolution due to any material used in processing.¹⁴

CELL BLOCK CYTOLOGY IN NON-ORAL LESIONS

Numerous studies have been carried out on cell block technique in non-oral lesions and they have shown mixed results. Most of the studies have recorded increased cellularity, even distribution of the cells, well preserved cellular and nuclear details, better architectural patterns, morphological features, staining characteristics, an additional yield of malignant cells and increased sensitivity.^{4,8-13,15-17} In few other studies, the conventional smears fared better than the cell block sections for routine diagnoses, mainly due to the superior preservation of cytoplasmic and nuclear characteristics.^{5,11,19} As observed by other investigators, the other benefit of cell block is concentration of cellular material in one small area that can be evaluated at a glance with all cells lying in the same focal plane of the microscope.^{4,17} Cell block can also be used for routine and special histochemical stains as it

can give well-stained positive results with no loss of tinctorial properties.⁹ IHC staining has shown better results with cell block. The lack of background and aberrant staining in cell block technique produces enhanced specimen quality, accurate diagnosis and diminished false negatives. Hence cell block is preferred technique over the smears for IHC studies.^{8,9,11,12} Due to the increased diagnostic yield provided by the cell block sections, it was suggested to use this technique as an adjunct to the conventional smear.^{7,10,13}

The cell block technique has been shown to be suited better for immunocytochemical (ICC) analyses.⁵ The ICC stains were superior on the cell block samples with absence of aberrant staining and background. It seemed that the conventional cell blocks and FNA smears complemented each other.¹¹

In a study, the findings were confirmatory in 60.3% cases of cell block preparation, and in 26.2% cases, the cell blocks provided additional information for diagnosis.¹⁸ It contributed additional information beyond what had been obtained from smears in 12% of cases, and in 44% of cases in which the smears were nondiagnostic.¹⁵ Of the 225 effusion fluids analyzed by both smear and cell block technique, 5 additional cases of malignancy in pleural fluids and 7 additional cases of malignancy in ascitic fluids were diagnosed with cell block technique, which could not be detected in the cytological smears, indicating that the cell block technique when used as an adjuvant to routine smear examination increases the diagnostic yield.¹⁰

The cell block method provided a diagnosis of malignancy in additional 4 patients in the benign group of patients with lung lesions, and the diagnosis of malignant effusion was increased by a ratio of 10%. Study in the malignant group, provided the subtyping of lung cancer in 7 patients.⁷

CELL BLOCK CYTOLOGY IN ORAL & PARAORAL LESIONS ODONTOGENIC LESIONS [TABLE 1]

Table 1: Cell block studies on cystic lesions of the jaw bones

Author & Reference Number	Year	Type Of jaw lesions Studied	Sample size	Techniques employed in the study	Results	Conclusion
Rivero et al [1]	2011	Cyst-like lesions of the jaw	17	CB, HP	47% cases diagnosed as OKC by CB Presence of keratin was diagnostic	Simple, fast and low-cost technique to effectively differentiate OKCs from other lesions
Oenning et al, [2]	2012	Jawbone lesions with cystic appearance	33	CB, HP	All 11 cases of OKC were diagnosed with CB	Fast, easy-to-handle, and low-cost technique for preliminary diagnosis of jawbone lesions
Melo et al [21]	2020	Odontogenic lesions and idiopathic bone cavities	52	CB, HP	The kappa coefficient of CB compared to HP was 0.390 to 0.612. Concordance	CB technique presented a high diagnostic usefulness for detecting RC and OKC

					<p> e rates between CB and HP for RC was 76.0% - 80.0%; OKC 58.8%- 76.5%; IBC 40.0%- 80.0% and UA 20.0%- 40.0% </p>	
Pallavi et al [24]	2019	odontogenic cysts and ameloblastoma	17	CB, Cytology, HP	<p> Diagnosis based on CB –OKC - 71.4% DC & RC - 66.7% Ameloblastoma -50%. </p>	CB gives accurate diagnostic architecture and apparent histopathological features
Hallikeri et al [25]	2021	Odontogenic lesions , MEC	51	CB, FNAC	<p> Agreement rate 74.5% to 56.8%; Additionally 5 cases of OKC and 1 case of MEC was detected. </p>	CB could be used as an ancillary technique to aid in definitive diagnosis of head and neck swellings.
Belatto et al [26]	2014	Ameloblastoma	9	CB, IHC	<p> Presence of epithelial cells showing positive staining to AE1/ AE3 and acellular amorphous eosinophilic materials </p>	Cytological findings, in light of clinical and imaging data, can be helpful in the presumptive diagnosis of ameloblastoma
Rivero et al [31]	2014	OKC	20	CB,HP	<p> 19 cases diagnosed as OKC, 1 case as OOC </p>	Very effective in the diagnosis of OKCs through parakeratin identification

In a study the application of the cell block technique as an adjunct method for likely diagnosis of aspirates from 17 cyst-like lesions of jaws was analyzed and compared to histopathological diagnosis. 17 cases of odontogenic cystic lesions including 7 cases of ameloblastoma were

taken. Both FNAC and Cell block were done and compared with histopathology. The cell block features were the presence of keratin in OKC, inflammatory cells in radicular cyst, epithelial cells in dentigerous cyst and epithelial cells of odontogenic origin in ameloblastoma. These findings were not appreciated in FNAC findings of the same cases. Hence, it was established that cell block technique is more specific and definite than FNAC. This technique can be used as a complementary preoperative diagnostic technique to aid in the development of a therapeutic plan for cystic jaw lesions.¹

The exfoliative cytology of keratinizing odontogenic tumor (KOT) demonstrated the presence of keratin in the cystic cavity. This finding is solid indication of KOT.² Viability of the cell block technique as an auxiliary method for diagnosing jawbone lesions was investigated in 33 clinically diagnosed cystic jawbone lesions. The aspirated material was processed by the cell block technique and compared with histopathology. Association was noted between cholesterol clefts and the cysts, KOT and epithelial cells, para keratin and KOT. A preliminary diagnosis of cystic lesions and KOTs could be made by the cell block technique. In cell block slides, the presence of cholesterol crystal clefts suggested cystic lesions and the presence of para keratin was highly suggestive of KOT, eliminating the need for incisional biopsy in the therapeutic planning for these lesions. The cell block technique proved to be easy-to-handle, fast and low-cost complimentary method for the preliminary diagnosis of jawbone lesions.² Similar conclusions were drawn in another study where in the presence of para keratin in 8 of the 17 cases by cell block technique established the diagnosis of keratocystic odontogenic tumors (KOTs), which was confirmed with histopathological analysis.¹

In another study, 52 cystic or cyst like jaw lesions were subjected to both FNAC and cell block analysis and compared with the histopathology findings by two separate group of individuals. The kappa coefficient of cell-block compared to histopathological diagnosis was 0.390 to 0.612. The highest concordance rates between cell-block and histopathological diagnosis were observed for radicular cyst (RC-76.0% - 80.0%) and odontogenic keratocyst (OKC-58.8% to 76.5%). Conflicting results were found regarding idiopathic bone cavities (IBC-40% to 80%) and unicystic ameloblastomas (UA-20% to 40%) which presented the overall lowest concordance rates. The authors concluded that the cell-block technique presented a high diagnostic usefulness for detecting RC and OKC and, if associated with clinical and radiographic characteristics, might be sufficient for final diagnosis of these lesions. Regarding IBC and UA, an analysis with a higher number of cases was recommended.²¹

The cell block method has been evidenced to be very effective in differentiating KOTs from other lesions that demonstrate similar clinical and radiographic characteristics, or with unusual features through para keratin identification. This feature is very useful especially in cases with severe inflammation that may affect the walls of KOT, causing epithelial metaplasia of cystic lining and loss of their typical characteristics.^{1,2} Cell block method can be used for differentiating some of the benign tumors that may present with a cystic degeneration, such as ameloblastoma, odontogenic adenomatoid tumor and ameloblastic fibroma.^{1,2,22} Centrifugation of the aspirated liquid from these extensive benign lesions can improve the diagnosis due to the concentration of lesion-typical cells.²³

17 cases of odontogenic lesions were studied with FNAC and cell block technique. Of the 17 cases, 71.4% odontogenic keratocyst, 66.7% dentigerous cysts, 66.7% radicular cysts and 50% ameloblastomas showed positive results with cell block technique. Cell Block was found to be a novel diagnostic preoperative technique in oral pathology for odontogenic cysts, tumors, metastatic tumors and bony lesions. It provides accurate diagnostic architecture and apparent histopathological features Compared to FNAC. This technique can be used alternative to FNAC.²⁴

51 cases, including 49 odontogenic lesions, 1 each of intra osseous mucoepidermoid carcinoma (MEC) and adenomatoid odontogenic tumor were studied with FNAC and cell block technique. While there was an agreement of 56.8% with the biopsy reports for cytology, it was 74.5% for cell block. On cytological examination, 7 OKCs and 22 radicular cysts were diagnosed, whereas ameloblastomas, AOT, intraosseous MEC, and dentigerous cysts were not. In cell block sections, 12 OKCs, 22 radicular cysts, 1 MEC, and 3 cases of ameloblastoma were diagnosed in accordance with the histopathology, while dentigerous cyst and AOT failed to do so. The architectural pattern and the morphology of the cells were better preserved by the cell block technique in comparison with FNAC.²⁵

9 Cases of ameloblastoma when studied under CB, showed the presence of epithelial cells and acellular amorphous eosinophilic materials in most of cases. These cytological findings, along with the absence of cholesterol crystal clefts or keratin, and the clinical and imaging data support the presumptive diagnosis of ameloblastoma by eliminating other possibilities, such as inflammatory cysts or OKC. IHC with AE1/AE3 antibody showed positive staining of the epithelial cells.²⁶

MUCOSAL LESIONS

Cell block preparations from oral lesions provide excellent cytopathologic features compared to smears. A statistically significant difference was noted for CB compared to smears respectively for the following features - 87.8% and 71.1% for distinct cellular morphology 97.8% and 91.1% for nuclear morphology, 78.9% and 42.2% for staining qualities. The sensitivity, specificity, PPV, NPV and accuracy of the modified cell block compared to smears for assessment of cell morphology was 93.7, 26.9, 75.9, 63.6%, and 74.4%; for nuclear morphology 97.6, 00.0, 90.9, 00.0% and the 88.9%; for staining quality 28.8, 89.5, 78.9, 47.9% and 54.4%.²⁷

A special gelatine pocket suitable for paraffin embedding of sparse material obtained from brush biopsies was developed and a combined evaluation of both cytologic and histologic features was done. A total of 51, 755 brush biopsies from suspicious lesions of the oral cavity, mostly oral potentially malignant disorders were evaluated. Of all, 1.7% were positive, 78.2% were negative for any epithelial atypia, 16.8% atypical and 3.3% inadequate. A 'positive' diagnosis by cytohistology was a reliable indicator of dysplasia or carcinoma. In the 'atypical' category, a variety of lesions were found, about half being dysplasia or carcinoma. This category challenges the clinician for further clinical, therapeutic and/or excisional examination. In 'negative' cases with persistence of the lesion, a re-examination in 1-year sequence is recommended. Conclusion: Cytohistology of material derived by abrasive methods allows earlier detection of dysplasia/carcinoma.²⁸

TUMORS

Primary oral diffuse large B cell lymphoma (DLBCL) is a rare disease. Its low incidence, nonspecific symptoms and its resemblance to common oral diseases makes its differential diagnosis difficult. An effort was made to assess if an accurate diagnosis of DLBCL could be made using liquid-based cytology (LBC) and cell block (CB) for its morphological interpretation and cytohistological assessment. The large-size lymphocytes with large irregular nuclei and prominent nucleoli could be noticed in LBC, suggesting the existence of large B-cell lymphoma. The sub classification of activated B-cell phenotype of DLBCL could be established based on the immunohistochemical expression of CD10-/ B-cell lymphoma 6 (BCL6)+/ multiple myeloma oncogene 1 (MUM1)+, which is a significant risk factor in DLBCL, on the CB sections. The outcomes suggested that the combination of LBC and CB is a valuable and informative tool for making a precise molecular diagnosis of oral DLBCL in clinically suspected lymphomas.²⁹

SALIVARY GLANDPATHOLOGIES

1,009 non gynecological specimens including that of head and neck and salivary gland specimens were comparatively analyzed using smears and cell blocks. The cell block sections showed clearly recognizable normal and abnormal cells with minimal shrinkage and aberration. The cytomorphologic features were well maintained, and staining characteristics of the nucleus, nucleoli and cytoplasm were sharp with clear recognition of nuclear and cytoplasmic features. The intracellular details were equally sharp and clearly distinct. Routine histochemical stains and panel of immunohistochemical staining revealed well-stained positive results with no loss of tinctorial properties.⁹

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) showed an accuracy of 87.5%, sensitivity 45.8% and specificity 98.9%. specifically it was 98.4%, for diagnostic categories that included non-neoplastic, benign neoplasm and malignant neoplasm and it was 73.5% for undetermined categories which included atypia of undetermined significance, salivary gland neoplasm of uncertain malignant potential and suspicious for malignancy. The application of CB in the cytological diagnosis of salivary glands is beneficial as it aids in increasing diagnostic accuracy, patients' management and treatment.³⁰

DISCUSSION

CB can aid in an accurate presurgical diagnosis of ameloblastoma. The cell block sections of ameloblastoma show sheets of peripheral clumps of cuboidal to columnar tumor cells, tumor cells with peripheral palisading appearance and stellate reticulum. It is possible to observe the characteristic morphology of the tumor cells under CB sections. The ameloblastic cells can be seen arranged in cribriform and /or trabecular pattern. Areas showing squamoid differentiation and presence of cystic changes can be appreciated. Fibrous stroma having sparse chronic inflammatory cells can be present in some blocks. Presence of only inflammatory infiltrate will be non-diagnostic.^{23,25,31,32} Mucoepidermoid carcinoma will show the presence of benign round to ovoid cells in clusters with basophilic nucleus in a mucinous background and few mucous cells and inflammatory cells.²⁵

The cell blocks of radicular cyst will show fibromyxoid tissue, cholesterol clefts and epithelial cells. Presence of parakeratin in cell blocks of OKC is seen in all the cases and is highly diagnostic.^{21,25,32}

Cellular and nuclear morphology, staining quality and details of architectural pattern are well appreciated with cell block cytology technique compared to smears of the fine needle aspiration. Staining of the nucleus and cytoplasm will be sharp and clear.^{23,}

Definite diagnosis could be made easily with cell block for both benign and malignant conditions and the cell block method with immunostaining shows a higher diagnostic yield than smear cytology.¹² The studies have suggested that combining smear preparation with the cell block can combine the advantages of both approaches and produce an increased diagnostic accuracy.¹³ Enhanced specimen quality, accurate diagnosis and diminished false negative was recorded suggesting that cell blocks can aid in easy diagnosis of malignancies.⁸ IHC stains are shown to work better on the cell block samples due to absence of background and aberrant staining.

CONCLUSION

Cytology forms one of the important non-invasive economical methods in screening and diagnosis of pathological lesions. Alternatively, the cell block technique involves retrieving small tissue fragments, processed to form a cell block. It is one of the extensively researched and established technique in pathology due to its ability to provide increased cellular yield and improved diagnostic accuracy. It is well suited for immunostain studies and molecular

diagnosis too. It has been found that the cell block technique can be used as a new diagnostic preoperative technique for odontogenic cystic lesions, tumors, bony lesions and head-and-neck metastasis of squamous cell carcinoma, where FNAC is the present option. The literature on the role of cell block technique in oral pathology lesions is currently sparse and therefore a wide window of opportunity to explore and establish its application in these lesions awaits us.

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