Editorial

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Liquid-Based Cytology: A 25-Year Bridge between the Pap Smear and Molecular Cytopathology

Pio Zeppa

Department of Medicine and Surgery, University of Salerno, Salerno, Italy

Liquid-based cytology (LBC) was first applied to gynecological cytology almost 25 years ago [1]. A few years before, the conventional Pap smear, after decades of unquestionable success proven by the drop in morbidity and mortality rates due to cervical carcinoma in the countries that had adopted it in national screening programs, met some criticism in the international media. Because of a reported rate of false negatives and some inefficiencies, the Pap test was openly discussed and criticized in journals that were not usually devoted to specific scientific issues [2, 3]. The following and timely introduction of LBC aimed to improve the efficiency of gynecological cytology through procedure standardization, sample quality improvement, screening support and speedup, and quality control, as well as by storing the residual material for possible repetitions and/or the application of ancillary techniques. Whereas LBC seems to be neither more sensitive nor more specific than the conventional Pap test, mainly in the detection of high-grade cervical intraepithelial neoplasia [4], overall it achieved the above-reported goals, with its additional costs being compensated by reported advantages. As a consequence, LBC has replaced the conventional Pap smear in many laboratories in industrialized countries and promises to survive the era of cervical HPV testing and vaccination.

Since its introduction, many laboratories have started to apply LBC to exfoliative and aspiration nongynecological cytology, aiming to exploit the same advantages on different samples. In fact, LBC is well suited to meet the requirements of ancillary techniques and their routine application in pathology laboratories, with specific reference to procedure standardization, purification and storage of diagnostic material. As a matter of fact, method standardization and the opportunity to store cells are significant benefits of nongynecological LBC, which can be used in different organs for different applications. Whereas the advantages of gynecological LBC have been immediately obtained on respiratory cytology [5], the same features of LBC have limited, in some cases, the diagnostic criteria typical of traditional cytology. For instance, the additional value of collected material and the time saved from cytological assistance, mainly in CT-, EUS- and EBUS-guided FNA techniques, as well as other time-consuming FNA techniques, may hamper or even exclude the possibility of performing rapid on-site evaluation and the immediate repetition of inadequate samples. Moreover, at a diagnostic level, the clean and purified background that improves and enhances cellular details in gynecological LBC or in bronchial washing-brushing in thyroid and breast FNAs eliminates or re-

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E-Mail karger@karger.com
www.karger.com/acy

0001–5547/14/0586–0519$39.50/0

Correspondence to: Prof. Pio Zeppa
Azienda Ospedaliera Universitaria, San Giovanni di Dio e Ruggi d'Aragona
Largo Città d'Ippocrate n.1
IT–84100 Salerno (Italy)
E-Mail pzeppa@unisa.it

duces colloid and myoepithelial cells, as well as stroma fragments, which represent additional diagnostic criteria for goiter and fibroadenoma, respectively. Nonetheless, beyond the microscopic diagnostic criteria, procedure standardization and cell storage are the great advantages of nongynecological LBC, which can be exploited in different cytological fields for different requests and applications. In this issue of *Acta Cytologica*, readers are provided with a comprehensive and critical overview of LBC applied to different nongynecological samples and different technical procedures. In the article by Ren et al. [6], basic LBC technical procedures and cytological features of different samples of exfoliative and aspirative cytology are clearly and synthetically reported, providing an LBC taxonomic handout. Remarkably, some thin-layer-specific cytological features that highlight their differences from conventional smears (CS), such as lymphocytes artificial aggregation or fragmentation of cohesive epithelial cells, are clearly reported [6] and the possible final reconversion of residual material in cell blocks is also described. Breast FNA has been significantly reduced after the introduction of core needle biopsy. In addition to the impossibility of distinguishing in situ from invasive tumors or of correctly diagnosing papillary lesions, the main limitation of breast FNA is operator dependency, and LBC provides the opportunity to overcome this latter limitation. In the article by Gerhard and Schmitt [7], specific cytological criteria and diagnostic performances of breast LBC are analytically reported, showing that breast LBC sensitivity and specificity is equal to or, in some cases, even higher than CS values. The diagnostic 'equality' between LBC and CS is overcome by the advantages offered by LBC in terms of antigen preservation and the good reproducibility of HER-2 status by FISH or CISH in thin-layer and histological controls. As far as thyroid FNA is concerned, follicular lesions of undetermined significance may be considered the Achilles heel of the otherwise most successful thyroidal FNA. In the article by Rossi et al. [8], a comprehensive overview on the usage of HBME and galectin-3 on follicular lesions of undetermined significance is reported, where LBC proves to be an excellent tool for this purpose. With reference to molecular procedures, LBC has been conveniently used on thyroidal FNAs for tests that evaluate a wide panel of mutations [9, 10]. Moreover, the next-generation sequencing procedures that promise to further increase diagnostic sensitivity and specificity of thyroidal FNA will probably use routine LBC samples too [11]. As reported above, LBC may require different diagnostic criteria from those utilized on CS, as is the case with salivary gland tumors. In the article by Rarick et al. [12], LBC diagnostic criteria for salivary gland tumors are exhaustively described. Once more, LBC advantages may be exploited when FNA is performed by noncytopathologists and liquid suspended cells may be alternatively used for LBC or cell blocks when rapid on-site evaluation is performed [10]. Micronuclei (MN) are chromosome fragments or whole chromosomes that are excluded from the nucleus during mitosis. MN can be identified by the same nuclear staining and used to evaluate chromosomal instability in cancerous and precancerous lesions. MN evaluation of exfoliated buccal cells has been performed since the 1980s [13], mainly on people exposed to different environmental genotoxic agents. Ramos et al. [14] studied MN on exfoliated buccal cells in workers exposed to carcinogenic agents and demonstrated that LBC is an excellent tool for MN evaluation. Lung cytology has been the first nongynecological application of LBC [4]. Because of the similarities that bronchial washing and brushing share with gynecological cytology samples, LBC lung cytology has exploited the same advantages [5, 15]. In the article by Michael and Bedrossian [15], a detailed and analytical overview of LBC lung cytology is reported, including the evaluation and cost comparison of both ThinPrep and TriPath. Additional advantages of LBC lung cytology include the possible application of almost all the ancillary techniques. In the article by Bellevicine et al. [16], the authors confirmed the evidence generated by a previous validation study [17]. They reported the experience of an academic centralized laboratory demonstrating that LBC is suitable for EGFR analysis to select patients for targeted therapy in lung cancer [16]. In fact, in their practice, EGFR testing performance features on LBC such as the rates of sample adequacy and of mutant, overlapped with those generated by direct smears [17]. Finally, the article by Abedi-Ardekani and Vielh [18] provides an in-depth analysis by summarizing and critically reviewing the most important applications of molecular techniques to LBC. In conclusion, nongynecological LBC has an increasingly important role in diagnostic cytopathology. LBC has a similar or better diagnostic accuracy than CS provided that specific diagnostic criteria are applied. The possibility of storing additional material that is useful for molecular procedures provides LBC with a great advantage that promises to be further exploited by the next-generation sequencing technology, and promotes LBC as a reliable alternative tool to surgical or core needle biopsies in cancer diagnosis, prognosis and prediction.

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