

Induced sputum cell counts in medical practice

O escarro induzido na prática médica

Elcio Oliveira Vianna

Clinicians first became interested in analyzing the sputum of patients with asthma more than 100 years ago, when Curschmann's spirals and Charcot-Leyden crystals were described as being associated with the eosinophilia seen in such patients. However, sputum analysis did not prove to be relevant for therapeutic decision-making, or even for pathophysiological investigation, until the early 1990s. The advent that drove this recent upsurge in the use of sputum qualification as a parameter of airway inflammation was the development of a new technique. In this new technique, sputum is induced by submitting the patient to inhalation of hypertonic saline that has been ultrasonically nebulized. This procedure was initially employed in the investigation of *Pneumocystis jirovecii* in patients with AIDS.⁽¹⁾ Its use increased greatly when it began to be applied in asthma patients, after which it was fine-tuned in terms of the analysis of the samples obtained, and finally it was validated for use in various other respiratory diseases, which further increased the spread of use.⁽²⁾ International guidelines have addressed details ranging from the laboratory methodology to the risks to patients.^(3,4)

Therapeutic interventions for asthma have, to date, been based on the clinical profile and the spirometry results. However, since asthma is defined as having three components—obstruction, bronchial hyperreactivity and inflammation—why is it that only obstruction is given any weight? A similar question could be posed in relation to chronic bronchitis, the pathophysiology of which includes an inflammatory process that is given very little weight in medical practice, or even in relation to chronic obstructive pulmonary disease (COPD) or bronchiectasis. There are many answers to these questions, chief among which is the lack of a satisfactory method of evaluating inflammation in routine medical practice. Although various techniques have been proposed in order to meet this need, induced sputum is the one that has been the most widely studied and that has proven to be the most relevant in terms of guiding medical practice. The use of the induced sputum technique has improved the understanding of the relationship between pulmonary function and airway inflammation, has allowed different disease phenotypes to be identified, as well as defining how each of those phenotypes responds to treatment, and appears to have the capacity to inform deci-

sions regarding corticosteroid therapy in the treatment of asthma and COPD.^(2,5) There have been few studies demonstrating the role of sputum induction in the treatment of asthma, although there have been studies that imply its utility, showing that adjusting the treatment based on the evolving proportion of eosinophils in the sputum reduces the frequency of exacerbations.⁽⁶⁻⁸⁾

The article by Moritz et al., published in the current issue of the Brazilian Journal of Pulmonology, describes the protocol employed at a facility considered to be on the cutting edge of research into the induction and processing of sputum samples.⁽⁹⁾ The authors describe the use of sputum induction by five of their fellow pulmonologists, detailing the motives for ordering the procedure and the decisions made based on the results. The procedure was most often requested for the investigation of asthma, followed by chronic cough, bronchiectasis and COPD. In the majority of cases, the results prompted changes in the treatment regimen, principally in the corticosteroid dose. In addition, the authors provide an excellent review of the literature regarding the clinical scenarios in which sputum induction has become a routine part of the diagnostic and follow-up process. Furthermore they summarize questions related to the safety and success of the procedure.

The reader should bear in mind that the data presented by Moritz et al. reflect peculiarities of the treatment facility in question. Therefore, caution should be used in extrapolating these data to other national or international facilities, since the results obtained depend on the standardization of diagnostic and treatment protocols at each facility, as well as on the availability of other, competing, diagnostic protocols, the prevalence of a given disease in a given region, the screening process and patient referral procedures.

Moritz et al. also describe differences among the diseases evaluated in terms of the cytology of the sputum samples, thereby implying that the use of sputum induction is capable of detecting those diseases. However, the diagnostic utility of those differences is a topic which warrants further study, since a considerable proportion of the patients with COPD or bronchiectasis presented eosinophilic bronchitis, and 6% of the asthma patients presented neutrophilic bronchitis.

In the past, studies involving bronchoalveolar lavage and bronchial biopsy were limited in terms of patient sample

size. The advent of sputum induction allows us now to define more precisely the neutrophilic phenotype of asthma, as well as the implications of that phenotype, including the response to corticosteroid therapy, which has been shown to be less favorable in patients with non-eosinophilic asthma than in those with eosinophilic asthma.

The heterogeneity observed in the cytology of the sputum samples (eosinophilic in COPD and neutrophilic in asthma) probably indicates different phenotypes within each disease but might also signify a limitation of evaluating only expectorated leukocytes. This limitation is understandable, since cell migration is just one of the various components of diseases affecting the respiratory tract. The pathological anatomy of asthma, COPD and bronchiectasis presents characteristics other than neutrophilic or eosinophilic infiltration. In the case of asthma, in addition to the eosinophils, thickening of the basal membrane and epithelial desquamation are seen. Despite the fact that performing inflammatory cytology of induced sputum samples is the initial and a significant step, new parameters and new methods might still be needed in order to conduct more detailed studies of inflammation in our patients.

Regardless of the limitations and the successes already achieved, the induced sputum technique is still being tested in clinical studies designed to determine its relevance and therefore has not reached its apogee. Developments can appear in various forms, including the following: for improvement and standardization of the evaluation of mediators in the liquid (non-cellular) phase of the sputum; use of the cells for immunocytochemistry and culture (in vitro studies); processing without dithiothreitol (which affects cytokine concentrations); and combining the induced sputum results with those obtained using other methods of evaluating inflammation (assessment of expired air condensation and exhaled nitric oxide, as well as the identification of cellular and molecular markers in serum).

As character witnesses on behalf of the technique, we can state, based on the experience in our laboratory, that any researcher who has once used the induced sputum technique to investigate inflammation will be reluctant to plan future studies involving bronchoscopy, especially if the study subjects are at increased risk for bronchospasm. The Moritz et al. study characterizes the results of the

examination of induced sputum samples as a parameter of inflammation to be used in clinical practice and describes conditions under which the induced sputum technique should be included as part of the routine pulmonology workup. These scenarios in which the use of the technique is indicated will soon be assimilated into international guidelines related to the respective respiratory diseases.

Elcio Oliveira Vianna

Associate Professor in the Department of
Clinical Medicine

*Faculdade de Medicina de Ribeirão Preto
da Universidade de São Paulo – FMRP/USP,
University of São Paulo at Ribeirão Preto
School of Medicine – Ribeirão Preto, Brazil*

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