

Induced sputum in the management of COPD: clinical implications

A. Zanini¹, S. Della Patrona¹, A.L. Facchini¹, A. Spanevello^{1,2}

ABSTRACT: *Induced sputum in the management of COPD: clinical implications. A. Zanini, S. Della Patrona, A.L. Facchini, A. Spanevello.*

Sputum induction can be used as a non-invasive technique to investigate airway inflammation in asthma and COPD. We reported the case of a 68 year old man with COPD, stage III GOLD, that underwent sputum induction during two exacerbation episodes. The first cell count showed a typical sputum neutrophilia, whereas the second showed

sputum eosinophilia. On the basis of sputum cellularity, we decided to treat the first episode with a course of antibiotics and the second exacerbation with a course of antibiotics and oral steroids. The patient showed improvement in both cases, obtaining clinical stabilisation. The induced sputum cell count could be a useful technique in a clinical setting to evaluate the cellular characteristics of airway inflammation during COPD exacerbation and modulate the antiinflammatory therapy. *Monaldi Arch Chest Dis 2012; 77: 1, 23-25.*

Keywords: COPD, Airway inflammation, Induced sputum.

¹ Division of Pneumology, Fondazione S. Maugeri, IRCCS Rehabilitation Institute of Tradate (Varese),

² Department of Respiratory Diseases, University of Insubria, Varese, Italy.

Correspondence: Dr. Andrea Zanini, Fondazione Salvatore Maugeri, Via Roncaccio 16, 21049 Tradate (VA), Italy; e-mail: andrea.zanini@fsm.it

Introduction

COPD has been increasingly recognised as a chronic inflammatory disease characterised by sputum neutrophilia and, in some cases, eosinophilia [1]. Use of induced sputum cell counts has been largely proposed as a non-invasive technique to investigate airway inflammation in asthma and COPD [2, 3]. The technique of sputum induction allows the study of COPD patients during exacerbation as it is safe and well tolerated [4]. Neutrophilic inflammation is further increased during exacerbation [5]. Moreover, the presence of eosinophilic inflammation can be detected during exacerbation in subjects with COPD. Sputum eosinophilia identifies a subgroup of patients who particularly respond to corticosteroid treatment [6].

Case Report

A 68 year old man attended for routine review of his COPD complaining that he had recently been more breathless. His record reported a concomitant history of hypertension and hypercholesterolemia. He had a full-time commercial job with his wife. The man smoked ten cigarettes per day; he had a 25 pack-year history of smoking. He tried to quit smoking with the aid of nicotine patch, but his periods of abstinence had been short. He had two courses of antibiotics and oral steroids for exacerbations in the last 12 months. He produced copious sputum and chronic cough in the mornings. Current medications includes a salmeterol/fluticasone com-

ination inhaler, a tiotropium inhaler, ramipril, atorvastatin. On physical examination the lung sounded hyperinflated and had decreased breath sounds with some bilateral wheezes. The heart sounds were normal. A chest x-ray showed hyperinflation. Spirometry result: FVC 3.36 L (89% of predicted value); FEV₁ 1.38 L (47% pred.). Oxygen saturation was 96%. Induced sputum cell count at baseline: neutrophils 78%, eosinophils 3%.

Three months later the man attended to the out-patient office for urgent visit for COPD exacerbation (increase cough, increase purulent yellow/green sputum production, increased breathless). There were some crackles without wheezes on thoracic examination. Spirometry result: FVC 3.18 L (84% pred.); FEV₁ 1.20 L (41% pred.). Oxygen saturation was 92%. Induced sputum cell count: neutrophils 95%, eosinophils 1% (fig. 1). The man was treated with a course of antibiotics (Levofloxacin 500 mg/die - seven days) without oral steroids and continued his therapy with inhaled bronchodilators and steroids. Symptoms and the sputum purulence were reduced after 10 days; oxygen saturation was 95%.

Seven months later the man attended the ER for serious breathless and wheezing. The entity and the colour of the sputum did not significantly change. On physical examination there were an increased sounds mainly wheezes. Spirometry was not done and oxygen saturation was 90%. The patient was treated with inhaled salbutamol + ipratropium and theophylline + corticosteroids i.v. and a prescription of antibiotics (Levofloxacin 500 mg/day). The day after he attended our lab and

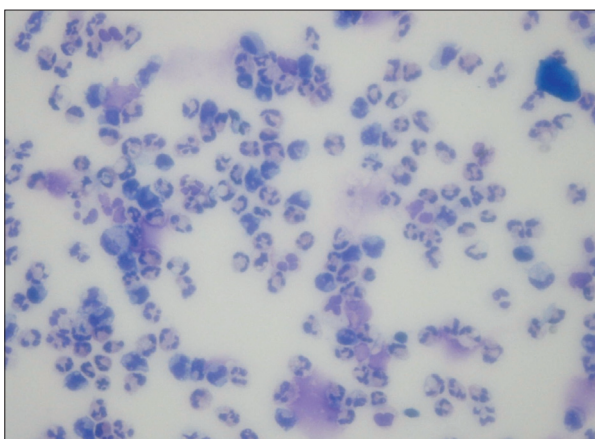


Fig. 1. - Induced sputum showing a high percentage of neutrophils (H & E Stain, 10X).

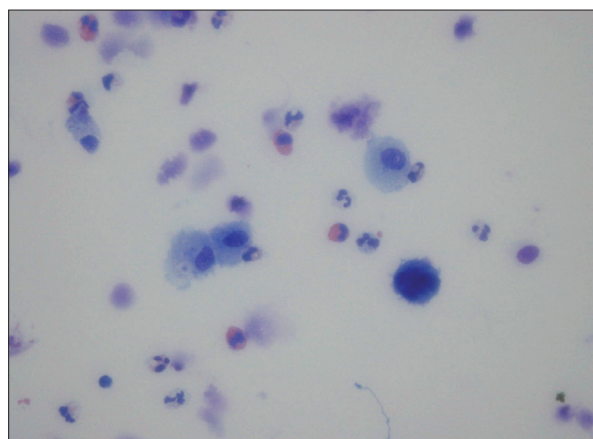


Fig. 2. - Induced sputum showing a high percentage of eosinophils (H & E Stain, 10X).

spirometry + induced sputum were performed. Spirometry result: FVC 3.40 L (90% pred.); FEV₁ 1.29 L (44% pred.). Oxygen saturation was 94%. Induced sputum cell count: neutrophils 74%, eosinophils 11% (fig. 2). The main causes of systemic eosinophilia – such as allergies (including allergic rhinitis and nasal polyposis), parasitic infections, neoplasms and immune disorders – were excluded. A course of oral steroids was started (Prednisone 25 mg/ die for seven days, then 12.5 mg/die for five days). Cough and wheezing were largely reduced after five days of oral steroids treatment.

One month later a sputum induction was performed: neutrophils 81%, eosinophils 3%. A schematic diagram of the case history reporting the clinical phases and the percentages of sputum cells is reported in figure 3.

The induced sputum cell count could be a useful technique in a clinical setting to evaluate the cellular characteristics of airway inflammation during COPD exacerbation and modulate the anti-inflammatory therapy.

Discussion

While chronic asthma is characterised by increased numbers of eosinophils in the sputum, COPD is characterised by increased numbers of neutrophils, although an increase in the numbers of neutrophils may also found in asthmatic patients [2, 3]. Many inflammatory mediators have been analysed in the fluid-phase of induced sputum. Several cytokines, chemokines, eicosanoids, markers of oxidative stress show an increase in COPD compared to asymptomatic smokers, with a further increase during exacerbations. Moreover, sputum fluid-phase in COPD shows an increase in neutrophilic granulocyte proteins and others molecules, that represent markers of neutrophil activation [5]. All these findings indicate that neutrophils are relevant in the pathogenesis of COPD, and there is a negative correlation between neutrophil count and the decline of FEV₁ [7].

We can use induced sputum to monitor inflammation in COPD. Interestingly, sputum cells were analysed on three separate occasions at four-weekly intervals [3]. Moderate, clinically stable COPD was associated with stable induced-sputum inflammatory markers, and the quantification of most cellular and soluble components is sufficiently reproducible [3]. Serial monitoring of inflammation in COPD using surrogate markers of induced sputum is a suitable tool for clinical routine, research purposes, and clinical trials. Additionally, sputum induction can be safely carried out in patients with mild-to-moderate COPD who

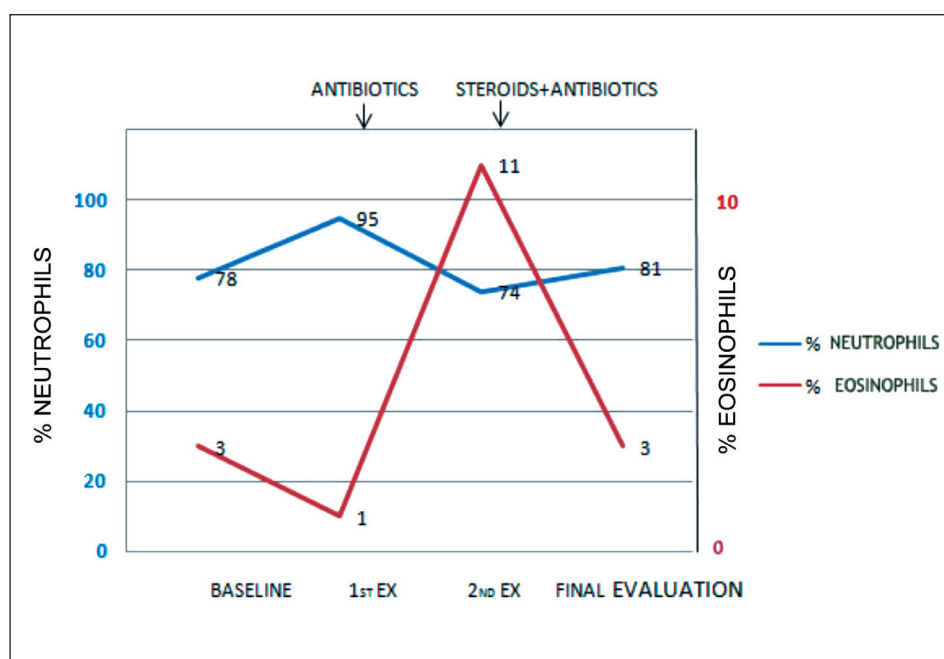


Fig. 3. - Schematic diagram of the case history reporting the clinical phases and the percentages of sputum cells.

experienced an exacerbation, and this occurs with no greater risk than in stable patients with COPD. This finding is very important, considering that acute exacerbations play an important role on the natural history of COPD. Bathoorn *et al.* performed sputum induction in COPD patients, both in the stable phase and during exacerbation [4]. In this study, the median FEV₁ for the stable phase and exacerbation were 61% and 51% of predicted, respectively, and the median decrease in FEV₁ with sputum induction during an exacerbation was 0.27 l vs 0.28 l during the stable phase [4].

Although COPD is mainly a neutrophilic airway disease, a substantial part of patients fitting the functional definition of COPD exhibit significant sputum eosinophilia (>3%) [8]. There is increasing evidence that the presence of sputum eosinophilia predicts an objective response to oral and inhaled corticosteroid treatment in COPD [6, 8-10]. Brightling *et al.* reported that the response in term of lung function to a two-week course of oral prednisolone increased as the baseline sputum eosinophilia count increased, and was associated with a marked treatment-induced fall in the sputum eosinophil count, but no change in sputum markers of neutrophilic inflammation [6]. Moreover, Siva *et al.* showed that a management approach over a 12-month period with the additional aim of reducing the sputum eosinophil count <3% using corticosteroids was associated with a 62% reduction in severe exacerbation of COPD requiring hospitalisation when compared to traditional symptom-based management [9]. Based on these reports, a measurement of sputum eosinophil counts could be used to identify COPD patients with corticosteroids responsive disease and to guide treatment.

References

1. Lacoste JY, Bousquet J, Chanez P, *et al.* Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 1993; 92: 537-548.
2. Spanevello A, Migliori GB, Sharara A, *et al.* Induced sputum to assess airway inflammation: a study of reproducibility. *Clin Exp Allergy* 1997; 27: 1138-1144.
3. Beeh KM, Beier J, Kornmann O, Mander A, Buhl R. Long-term repeatability of induced sputum cells and inflammatory markers in stable, moderately severe COPD. *Chest* 2003; 123: 778-783.
4. Bathoorn E, Liesker J, Postma D, Koëter G, van Oosterhout AJ, Kerstjens HA. Safety of sputum induction during exacerbations of COPD. *Chest* 2007; 131: 432-438.
5. Bhowmik A, Seemungal TAR, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000; 55: 114-120.
6. Brightling CE, Monteiro W, Ward R, *et al.* Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000; 356: 1480-1485.
7. Stanescu D, Sanna A, Veriter C, *et al.* Airways obstruction, chronic expectoration, and rapid decline of FEV₁ in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; 51: 267-271.
8. Pizzichini E, Pizzichini MM, Gibson P, *et al.* Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1998; 158: 1511-1517.
9. Siva R, Green RH, Brightling CE, *et al.* Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J* 2007; 29: 906-913.
10. Brightling CE, McKenna S, Hargadon B, *et al.* Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 193-198.



Pavia - Almo Collegio Borromeo